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Cardiac morbidity and mortality in patients with RASopathy syndrome: an european multi centric study

Calcagni G. (1), Limongelli G. (2), D'Ambrosio A. (1), Gesualdo F. (1), Digilio M.C. (1), Baban A. (1), Albanese S.B. (1), Versacci P. (3), De Luca E. (3), Ferrero G.B. (4), Agnoletti G. (4), Baldassarre G. (4), Banaudi E. (4), Marek J. (5), Kaski J.P. (5), Tuo G. (5), Russo M.G. (2), Pacileo G. (2), Milanesi O. (6), Messina D. (6), Marasini M, (7), Cairello F. (7), Formigari R. (8), Brighenti M. (8), Dallapiccola B. (1), Tartaglia M. (1), Marino B. (3)
Bambino Gesù Children's Hospital, Rome, Italy (1); Monaldi Hospital, II University of Naples, Naples, Italy (2); Sapienza University, Rome, Italy (3); University of Turin, Italy (4); Great Ormond Street Hospital for Children, London, UK (5); University of Padova, Padua, Italy (6); Giannina Gaslini Institute, Genoa, Italy (7); Sant'Orsola Malpighi Hospital, Bologna, Italy (8)

Introduction: A detailed characterization of cardiac morbidity and mortality in RASopathies is lacking.
Methods: A multi-centric, observational, retrospective cohort study was conducted in seven cardiac centers to systematically collect and analyze available data on cardiac involvement, morbidity and mortality. The clinical records of 371 patients with confirmed molecular diagnosis of RASopathy were reviewed. Mortality was described as crude mortality, cumulative survival and restricted estimated mean survival. Multivariable regression analysis was used to study the effect of each mutated gene on cardiac defects, number of interventions and risk of intervention.
Results: Cardiac defects were found in 80.3% of cases. More than half had pulmonary stenosis (PS), followed by hypertrophic cardiomyopathy (HCM) (27%) and atrioventricular canal defect (AVC) (4.4%). *RAF1* mutations were the best predictors of cardiac involvement in the study population. *RAF1* and *BRAF* mutations were positively associated with HCM, while *PTPN11* defects with AVC and, less robustly, with PS. Among patients with heart disease (n=298), almost half underwent a percutaneous and/or surgical intervention. Mortality was relatively low, less than 3%. Among patients with HCM, those with age < 2 years and young adults were at higher risk for fatal events, which were related to their cardiac involvement in most of the cases, while those with biventricular obstruction and carrying *PTPN11* mutations had higher risk of cardiac death. Overall, crude mortality was 0.29/100 patients-year. Cumulative survival was 98.8%, 98.2%, 97.7%, 90.2%, at 1, 5, 10, and 25 years, respectively. Restricted estimated mean survival at 25 years follow-up was 24.2 years.
Conclusions: in our cohort of patients with RASopathy, cardiac involvement was common, and required percutaneous or surgical intervention in almost half of cases. The risk of intervention was higher in individuals with Noonan syndrome and PS carrying *PTPN11* mutations, and lower among patients with Costello syndrome and cardiofaciocutaneous syndrome. Mortality was relatively low in RASopathies. However, the association between HCM, a subset of *PTPN11* mutations, with a peculiar age distribution (infants and young adults), and the coexistence of left and right side obstruction, may predict early mortality, including immediate post-operative events and life-threatening events as sudden death.