32

Late Mortality in a Genetic Subtype of Tetralogy of Fallot

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Background: 22q11.2 deletion syndrome (22q11.2DS) is a common genetic subtype of tetralogy of Fallot (TOF). Past research suggests that TOF patients with a 22q11.2 microdeletion have increased mortality in pediatric populations. However, the impact on mortality in adult patients is unknown. **Methods:** We studied an adult cohort of 600 TOF patients, 72 with 22q11.2DS and 528 non22q as determined by genome-wide microarray. This sample was used to evaluate the impact of a 22q11.2 microdeletion on adult mortality while accounting for other factors. Analysis was done using a Cox proportional hazards regression that included cardiac anatomy, type of TOF repair, sex, and age at ascertainment as variables. **Results:** A greater proportion of patients with 22q11.2DS had pulmonary atresia (p=0.0006) or absent pulmonary valve (p=0.0007). Despite being significantly younger (mean age 33.2, SD 10.1 vs 43.3, SD 13.7; p<0.0001), mortality in 22q11.2DS was almost 3-fold greater than in non22q patients (18.1% vs 6.8%, p<0.0011), and 22q11.2DS patients died on average 16.5 years younger (p=0.0135). The presence of a 22q11.2 deletion was a significant predictor of mortality in adult TOF patients (PE= 1.866, HR= 6.462, p<0.0001). **Conclusions:** The results suggest that the 22q11.2 deletion significantly contributes to premature mortality in adults with TOF, mediated only in part by innate cardiac complexity. These findings suggest that molecular subtyping is likely to be an important factor for predicting late outcome in TOF.