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Genotype-Phenotype correlations in pediatric SCN5A mutation carriers: new insights for a better risk stratification

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Introduction: Genotype-phenotype correlations of SCN5A mutations remain unclear. Given the relative rarity of cardiac sodium channelopathies in the pediatric population, risk stratification in the young diagnosed with a given SCN5A mutation need to be clarified.

Methods: A multicenter, international, 1990-2015 retrospective cohort study was conducted in 25 tertiary hospitals in 13 different countries. All patients 16 years of age or younger diagnosed with a genetically confirmed SCN5A mutation, whatever the clinical diagnosis were included in the analysis.

Results: 423 children fulfilled the study inclusion criteria, with a median age of 7.6 (0.0-16.7) years at diagnosis; 34.7% individuals were probands. Phenotypic spectrum was divided in 76 (18.0%) isolated LQT3, 33 (7.8%) isolated BrS type 1, 86 (20.3%) isolated PCCD, 3 (0.7%) isolated SSS and 102 (24.1%) overlap phenotypes; 123 (29.1%) kept a negative phenotype throughout follow-up. The risk of arrhythmic events in children was high, especially when a spontaneous BrS, LQTS, PCCD or overlap phenotype was displayed but also in those with a negative phenotype. Phenotype varied according to mutation type, missense pathogenic mutations being more frequent than radical mutations or variants of unknown significance in isolated LQT3, isolated PCCD and negative phenotype patients. Cardiac arrest or syncope as first symptom as well as appropriate ICD shocks in implanted patients were more frequently observed in case of mutation located to the transmembrane region. Compound genotype, double SCN5A mutation, sinus node dysfunction, age ≤1 year at diagnosis and absence of family history of BrS, LQTS, PCCD or PM implantation and cardiac arrest or ICD implantation were independent predictors of cardiac event giving new insights to identify high-risk subgroups in SCN5A mutation-positive infants and children.

Conclusion: In the largest series of SCN5A mutation carriers children, we found a high rate of cardiac events; ECG phenotype varied according to mutation type, whereas clinical severity was related to mutation location; several factors emerged as predictors of cardiac arrest or arrhythmic event.