

Diagnosis of Congenital Long QT Syndrome: Do all Clinically Suspected Patients warrant Genetic Testing?

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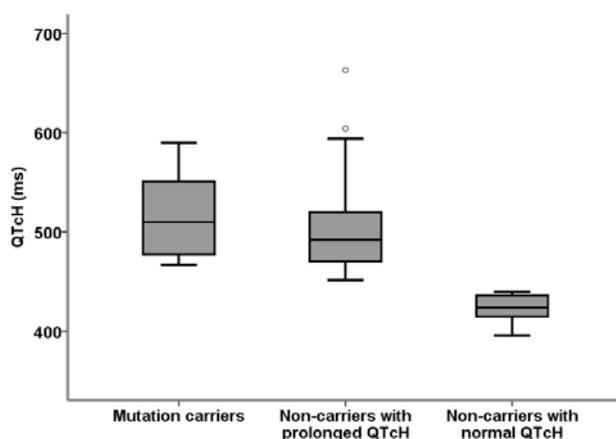
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Introduction: Diagnosis of congenital long QT syndrome (LQTS) involves clinical, electrocardiographic (ECG) and genetic evaluation. Genetic testing however has the disadvantage of not being uniformly available and is costly and time-consuming. This study aimed to investigate if all clinically suspected patients warrant genetic testing.

Methods: Study population included 214 unrelated probands referred for genetic counselling and predictive testing (KCNQ1/KCNH2/SCN5A/KCNE1/KCNE2/KCNJ2). Demographic and clinical characteristics, resting heart-rate and QTc from the earliest available pre-therapy ECG, Schwartz score (SS) and genotyping results were documented for all patients. Maximum QTc on Holter (QTcH) was analyzed for patients with a SS ≤ 3 . QTc/QTcH >450 ms were considered prolonged.

Results: Age at diagnosis was 31 ± 21 years (range 0-85 years), heart-rate 73 ± 19 bpm, QTc 478 ± 64 ms, 68% were female and 78% had symptoms suggestive of LQTS. KCNQ1/KCNH2/SCN5A/KCNJ2 mutations were present in 34/49/15/2 patients respectively. Among patients with SS ≥ 3.5 ($n=103$), 75% were mutation-carriers. Among patients ($n=111$) with SS ≤ 3 , QTc was prolonged in 32 (477 ± 20 ms, 28% mutation-carriers) and normal in 79 patients (417 ± 19 ms, 9% mutation-carriers). Among the latter 79 patients, QTcH was normal (425 ± 13 ms) in 16, all of whom did not carry a putative pathogenic mutation; QTcH was prolonged (506 ± 44 ms) in 63 patients, 7 of whom were mutation-carriers (Figure). Sensitivity and specificity were 83% and 79% for SS ≥ 3.5 in the total cohort, 56% and 76% for QTc cut-off 450 ms among subjects with SS ≤ 3 , and 100% and 22% for QTcH cut-off 450 ms in subjects with SS ≤ 3 and normal baseline QTc.

Conclusions: This study demonstrates that in the challenging group of patients with a clinical presentation suggestive of LQTS and a normal resting QTc, Holter QTc cut-off of 450 ms was 100% sensitive and can potentially be used to rule-out LQTS, especially when genetic testing is not readily available or feasible.



Maximum Holter QTc (QTcH) based on LQTS mutation-carriership in patients with normal baseline QTc (Open circles indicate outliers).