2:1 AV block due to extremely prolonged QT interval in newborns: variable genetic background

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Background
Three newborns presented with bradycardia and 2:1 AV block caused by markedly prolonged QT interval. Their parents were healthy with normal ECG’s.

Methods and results
Patient 1 was born with 2:1 AV block due to prolonged QTc-interval of 640 ms. Intermittent bradycardia had been observed since the 20th gestation week. Propranolol was started and 1:1 AV conduction was restored. At the age of 4 months, she had seizures and hypsarrhythmia on EEG. Her neurological development was slightly delayed. At 3 years she had syncope during exertion and deep bradycardia during sleep. On echocardiography and MRI, non-compaction cardiomyopathy with LVEF of 20 % was diagnosed. She underwent left cardiac denervation and epicardial DDD pacemaker implantation, and showed episodes of torsades de pointes (TdP) during recovery. Cardiac transplantation was considered, but the patient developed cardiac ischemia with hemodynamic compromise and did not respond to resuscitation. Exome sequencing revealed F142I de novo -mutation in CALM1 (calmodulin1) gene disrupting calcium signaling in cardiac cells. The combination of calmodulin defect with non-compaction cardiomyopathy is a new finding.

Patient 2 had 2:1 AV conduction in utero. Postnatally, QTc was 650 ms with T wave alternans and intermittent 2:1 conduction. There was no syndactyly. Echocardiography showed non-compaction cardiomyopathy. An epicardial DDD-pacemaker was implanted, and propranolol therapy 4 mg/kg/day was instituted. At the age of 6 weeks she died suddenly. Non-compaction cardiomyopathy was confirmed in pathologic specimens of the heart. LQT8 (Timothy syndrome) was diagnosed with de novo G406R mutation in CACNAC1 gene.

Patient 3 had intermittent AV block in utero. After birth 2:1 AV conduction and QTc of 530 ms were observed. Repetitive TdP bursts were controlled with esmolol infusion and later with propranolol. VVI-pacing was instituted at the age of 2 weeks and upgraded to DDD-pacing at 4 years. She is doing well. A homozygous LQT2 gene defect L552S (Finnish founder mutation) was diagnosed.

Conclusions
Newborns with 2:1 AV conduction and extremely prolonged QT have poor prognosis. Two of our three patients died; both had also non-compaction cardiomyopathy. One death was probably arrhythmogenic, the other one due to ischemia. Genetic testing may provide exact diagnosis.