

A Unique case of Timothy Syndrome due to coexistence of CACN1C and Ank2 mutations

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Introduction: Timothy Syndrome is a very rare and fatal type of ion channel disease in which dysmorphic features are together with rhythm abnormalities. Mutations of CACNA1C gene are reported in the etiology. Ankyrine2 mutation is found in LongQT4 Syndrome. We present a case of Timothy Syndrome with two different mutations of CACNA1 and Ank2 genes.

Case: Six-day-old boy was consulted for bradycardia. He had respiratory distress requiring positive airway pressure support starting at the first day of life. On the 4th day intermittent bradycardia of 52/minutes was noticed which could increase up to 120/minutes. Birth weight was 2600gr. And low for gestational age. Physical examination revealed heart rate as 65/minute. blood pressure 80/40 mmHg, arterial oxygen saturation 94%. Syndactyly of fingers 3 through 5 of left hand and 4 and 5 of right hand were found. He had bald head, round face, flat nasal bridge and thin upper lip (figure 1-2). His lower limbs were in plaster cast because of pes equinovarus, syndactyly of the toes could not be observed. Electrocardiogram showed a heart rate of 60/minutes, 2:1 atrioventricular block and prolonged QT interval (QTc = 720 msn) (figure 3). Echocardiography revealed atrial septal defect, patent ductus arteriosus and pulmonary hypertension (right ventricular pressure was estimated as 78 mmHg using the tricuspid regurgitation jet velocity). The parents were consanguineous, history of sudden cardiac death, arrhythmia or LQTS were absent in the family. Propranolol and inhaled iloprost treatments were started. Implantation of an ICD system was planned. However, within the following day the patient had sudden cardiac arrest and did not respond to resuscitation.. Genetic analysis revealed compound heterozygous c.4418C>G (p.Ala1473Gly) mutation in exon 38 of CACNA1C gene and c.11791G>A (p.Glu3931Lys) mutation in exon 45 of ANK2 gene. Both parents were negative for CACNA1C mutation and mother was carrier for Ank2 mutation.



Figure-1

Figure-2

Figure-3

Conclusion: This is the first report with unique coexistence of CACNA1 and Ank2 mutations in Timothy phenotype causing fatal outcome.