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Letter to the Editor

Abnormal electroencephalogram, epileptic seizures, structural congenital heart disease and aborted sudden cardiac death in Andersen–Tawil syndrome

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Andersen–Tawil Syndrome (ATS) is type 7 of congenital LQTS and is caused by mutations in the gene *KCNJ2* that encodes a protein that forms the rectifier potassium channel $K_{ir}2.1$ [1,2]. ATS is characterized by periodic paralysis, ventricular arrhythmias, prolonged Q–U interval, and mild facial or skeletal abnormalities [3–5]. Sudden cardiac death (SCD) has been increasingly reported [6]. A very small number of ATS cases with seizures have been previously reported [7–9]. A case of ATS with aborted SCD, molecular confirmation, and two relevant associations: epilepsy and congenital heart disease (mitral valve prolapse) is presented. The association of severe congenital mitral valve disease requiring surgery has not been reported before in ATS.

A 7-year-old Mexican mestizo girl was evaluated due to her twin sister's sudden death. She had history of 6 episodes of syncope. Physical examination showed triangular facies and micrognatia (Fig. 1A, B), arrhythmic heart sounds and murmur of mitral insufficiency. Laboratory exams showed hypokalemia. Her 12-lead ECG (Fig. 1C) showed sinus rhythm, prominent U wave, QT/QTc 409/510 ms, and ventricular premature beats (VPB). Holter monitoring confirmed very frequent VPB (41,192/24 h), with multiple morphologies, couplets, bigeminy, and several episodes of non-sustained ventricular tachycardia. Severe mitral regurgitation secondary to prolapse of the anterior leaflet was confirmed (Fig. 2A, B). She underwent uncomplicated mitral valvuloplasty and was discharged with potassium supplementation. After surgery, the number of fainting episodes was substantially decreased. Initially, the diagnosis of ATS was not suspected and she was given amiodarone and later sotalol without effect on VPB. Four years later, when the diagnosis of ATS was suspected, a detailed clinical examination revealed short stature, slow weight gain, large forehead, abundant eyebrows, downward slanting palpebral fissures, flat nasal bridge, bulbous nose, malar and mandibular hypoplasia, dental crowding, low set ears, clinodactyly of the fifth fingers of both hands, and cutaneous syndactyly. Using massive sequencing sponsored by Sistemas Genómicos® (Valencia, Spain) in three different genes for LQTS, it was identified a pathogenic mutation in the *KCNJ2* gene, which changes an arginine by tryptophan at residue 218 in the protein, affecting interaction between $K_{ir}2.1$ and phosphatidylinositol-4,5-bisphosphate (PIP2), which makes $K_{ir}2.1$ enters an extra-long closed state [1]. A variant of unknown significance (rs201861473) in the *CACNA1C* gene was also identified. Once the diagnosis was confirmed, she was given flecainide (up to 5 mg/kg/day) without any relevant decrease in VPB. Under this treatment, she presents syncope suggestive of a vasovagal origin as it was preceded by dizziness and blurred vision, with no palpitations or cyanosis. When she arrived to the Emergency Department, 5 min later, she was found in sinus rhythm and was hospitalized. Twelve days later, still hospitalized, another syncope occurred. This time with generalized seizures. Due to the seizures, an electroencephalogram (EEG) was performed and considered frankly abnormal (Fig. 3), the brain MRI was normal. Instructions were given to take diphenylhydantoin and flecainide but the relatives never give it to her, she only received potassium supplementation. One year later she had another syncope, without premonitory symptoms and with facial traumatism. Therefore she underwent EP study. No VT/FV could be induced and the burden of PVB was so low that they could not be mapped; interestingly PVB diminished with isoproterenol infusion. An implantable loop recorder

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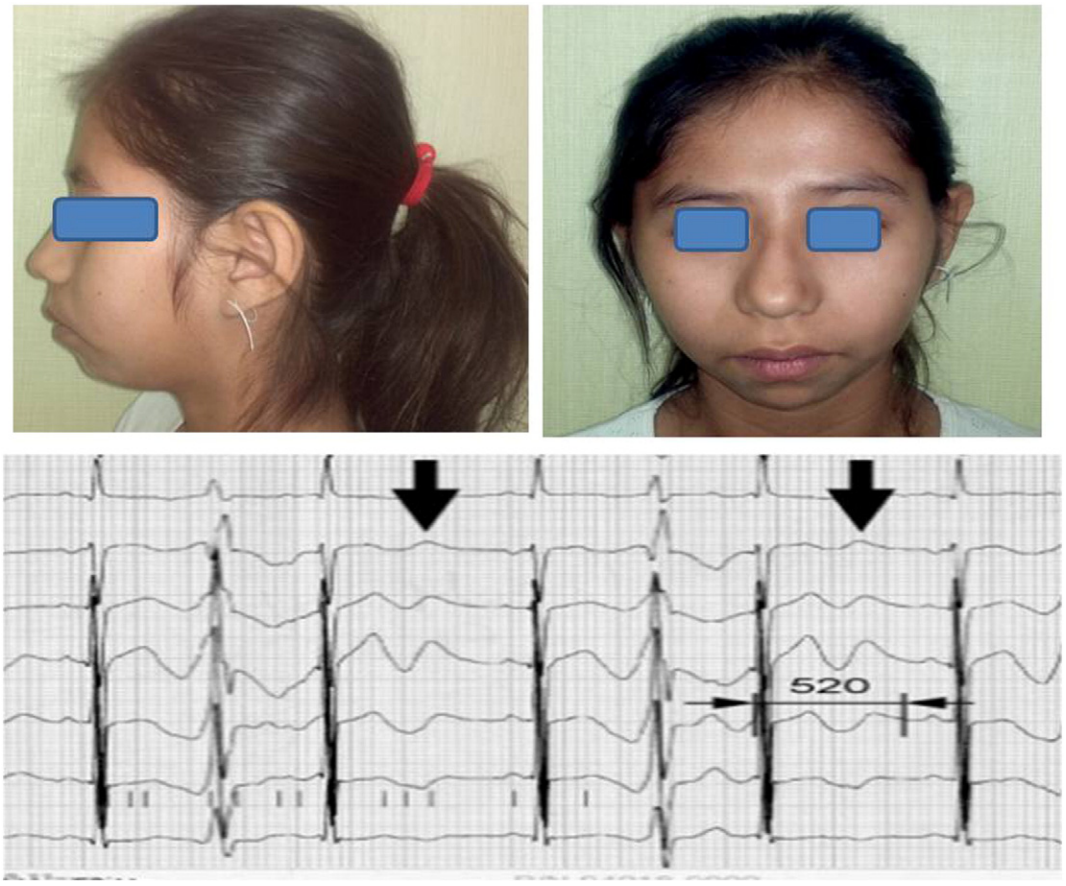

Fig. 1. Left lateral (A) and frontal (B) photographies of the index case. Baseline 12-lead ECG (C), only precordial leads are shown for clarity, showing frequent PVC (asterisks) and large U waves (arrows).
Reproduced with permission from Márquez et al. [1].

(Reveal, Medtronic, USA) was placed. Syncope recurred 9-months later and the recorder demonstrates a VT (torsades de pointes) and therefore, a cardioverter defibrillator was implanted.

Herein, a girl affected with ATS1 (genetic confirmation of *KCNJ2* mutation) with mitral valve prolapse, syncope, SCD and epileptic activity demonstrated by an abnormal EEG is reported. LQTS is an unusual but definite cause of pseudo-seizures. Recent numbers indicate that approximately 66% of patients with LQTS that report a seizure or seizure-like episode could be related to cerebral hypoperfusion due to ventricular arrhythmias rather than epilepsy as they did not demonstrate epileptic activity on an EEG [10].

It also has been informed the possible coexistence of true seizures in LQTS patients. A seizure phenotype was found more common in LQT2 and the authors called it a "LQT2-epilepsy association" [11]. This possibility has been further explored based on the fact that epilepsy has been found to be related to mutations of specific genes. The association between LQT genes and seizures has been delimited in the last years by several investigators for *SCN5A*, *KCNH2* and *KCNE2* genes, not only mainly with case reports but also with some cohort studies [12]. Haugaa et al. [13] reported on a cohort of LQTS secondary to a potassium channel mutation. Although none of the patients of the LQTS group had definite epileptic activity in the EEG, these recordings were abnormal in 71% (12/17) of patients with LQTS, in comparison with 2 of 16 healthy controls (13%). More recently, a prevalence of epilepsy of 1.6% (10 of 610) was reported among patients with LQTS [10].

The only three previous reports of true seizures in ATS are from Mexico, Japan and Spain. Canún et al. [7] reported a proposita who was born by cesarean section because of fetal distress after an uneventful pregnancy. At 9 months, she had vomiting and diarrhea associated with tonic–clonic seizures for 40 min. Seizures not related to fever occurring only in infancy were reported in 4 out of 23 (17%) patients of a Japanese cohort with ATS [8] and in Spain, one patient was reported with an isolated episode of seizures when he was 18-years-old [9]. Seizure activity and long QT interval may be both due to the dysfunction of $K_{ir}2.1$ or an association to other subunits of the K_{ir} family channels. Patients with mutations in the *KCNJ2* gene are frequently associated with deficits in executive function and abstract reasoning, suggesting that the clinical phenotypes of ATS may involve the central nervous system (CNS) [2]. These findings in conjunction with the present report support the notion that ATS, as well as other LQTS, may indeed must be considered a cardio-cerebral syndrome [12].

Another clinically relevant finding in the patient herein reported is the presence of congenital heart disease. Previous reports of congenital heart disease in ATS include pulmonary stenosis, bicuspid aortic valve, with and without coarctation [14], and atrial septal defect [15]. Only one previous case with minor mitral valve prolapse and trivial regurgitation has been reported [16]. Congenital mitral regurgitation requiring surgery has not been reported before. Echocardiographic screening for valvular heart disease would help to delimit the frequency of heart valve disease in this entity.

In summary, ATS was diagnosed in a 7-year-old mestizo girl with a mutation confirmed in *KCNJ2*. Relevant associations found were: congenital mitral regurgitation, syncope, aborted SCD and seizures. The presence of abnormal EEG supports the increasing amount of evidence of a "cardio-cerebral" ion channel dysfunction in LQTS.

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