Drugs of the Future 2008, 33(8): 701-704

CCC: 0377-8282/2008
DOI: 10.1358/dof.2008.033.08.1234826

Andersen-Tawil syndrome

C. Dulsat, N. Mealy
Prous Science, Provenza 388, 08025 Barcelona, Spain

CONTENTS

Abstract

Andersen-Tawil syndrome (ATS) is a rare inherited disorder linked to multiple mutations in distinct regions of *KCNJ2*, a gene that encodes potassium channels. ATS is characterized by extremely variable expression of a triad of phenotypes associated with *KCNJ2* gene mutations: periodic paralysis, cardiac arrhythmias and developmental dysmorphisms. More recent clinical investigations have also identified neurocognitive deficits associated with ATS. Randomized, controlled clinical trials of potential therapeutics for ATS are limited to date, although case reports of antiarrhythmics, carbonic anhydrase inhibitors and calcium channel blockers as pharmacological candidates are emerging.

Introduction

Andersen-Tawil syndrome (ATS), also known as Andersen syndrome or long QT syndrome 7, is a disorder that causes episodes of muscle weakness (periodic paralysis), changes in heart rhythm (arrhythmia) and developmental abnormalities (1, 2). ATS was first described by Andersen and colleagues in 1971 (3), and while its incidence is still relatively unknown, the clinical description of this rare inherited disorder continues to evolve as more affected families come to light. ATS has been linked to mutations in the *KCNJ2* gene which codes for a voltage-gated potassium channel, leading to the classification of ATS as a channelopathy. This review summarizes the clinical aspects of ATS along with the genetic and molecular basis of the disease and an update on current therapeutic developments.

Pathophysiology and genetics

ATS is inherited in an autosomal dominant pattern and exists as two types, defined by genetic cause: type 1 accounts for about 60% of all cases and is caused by dominant negative mutations in the *KCNJ2* gene (4, 5); the remaining 40% of cases are designated as type 2, the cause of which is unknown.

The *KCNJ2* gene encodes the inward-rectifying potassium channel known as $K_{ir}2.1$. This channel transports positively charged potassium ions across plasma membranes at negative voltages, aiding regulation of the resting membrane potential in neurons, cardiac and muscle myocytes (6). *KCNJ2* also encodes the main component of the inward-rectifier current (IK_1), which is involved in late-phase repolarization during the cardiac action potential (7). Loss of function of *KCNJ2* reduces IK_1, causing prolongation of the action potential duration (APD) in cardiac myocytes and increasing the potential for arrhythmias (5, 8, 9). In contrast, gain-of-function mutations in *KCNJ2* increase IK_1, reduce APD and may cause the short QT syndrome or atrial fibrillation (10).

Multiple mutations have been identified in distinct regions of *KCNJ2* in ATS patients (4, 11-14). Mutations in the *KCNJ2* gene alter the usual structure and function of potassium channels or prevent the channels from being inserted correctly into the cell membrane. Many mutations prevent binding of *KCNJ2* to the second messenger phosphatidylinositol-4,5-bisphosphate (PIP2), an essential process for activation of the ion channel and stabilization in its open state (13). These changes disrupt the flow of potassium ions in skeletal and cardiac muscle, leading to periodic paralysis and irregular heart rhythm, symptoms characteristic of ATS.

Clinical characteristics of ATS

Clinical variability of ATS was first described by Tawil and colleagues in 1994 (15), characterized by extremely variable expression of a triad of phenotypes associated with *KCNJ2* gene mutations: periodic paralysis, cardiac arrhythmias and developmental dysmorphisms. Heteromerization of the mutant $K_{ir}2.1$ with the other subunits $K_{ir}2.2$ and $K_{ir}2.3$, which are also found in the human heart, has been proposed to contribute to the variability of patient phenotypes (16). The Office of Rare Diseases and the Rare Diseases Clinical Research Network are currently undertaking a multicenter study across the U.S., Canada and the U.K. to better characterize ATS (17).

Dysmorphic features

Dysmorphic traits are often the first clue to ATS diagnosis and typically affect the head, face and limbs. The most common dysmorphic features found on clinical examination are broad forehead, hypoplastic mandible, hypotelorism (abnormally close eyes), low-set ears, abnormal curvature of the fingers (clinodactyly), fusion of 2-3 toes (syndactyly) and abnormal smallness of the head (microencephaly). Additional findings include abnormal or absence of lateral incisors, high-arched palate, cleft palate, short stature, abnormal curvature of the spine (scoliosis) and small hands and feet. These abnormalities are relatively consistent among patients; however, less apparent is the mechanism by which mutations account for the typical facial and skeletal abnormalities (1-3, 18-20).

Periodic paralysis

One of the earliest presenting symptoms of ATS is episodic muscular weakness, or periodic paralysis, that can last for hours or days and can arise spontaneously, although it more commonly occurs following a period of intense/prolonged physical activity. The reported prevalence of periodic paralysis in ATS patients is 64-83%, with onset usually recorded during adolescence and evidence for a reduction in the frequency and severity of episodes with age. Periodic paralysis does not appear to be related to serum potassium levels, as hyperkalemia, hypokalemia and normal serum potassium levels have all been recorded during episodes of periodic paralysis (1, 15, 21, 22).

Katz and colleagues have proposed that an electrodiagnostic 'exercise test', based on the measurement of compound muscle action potential amplitudes immediately after 2-5 min of intermittent voluntary contraction (23), could be used to diagnose periodic paralysis in ATS (24).

Cardiac manifestations

The most common changes affecting the heart in ATS are ventricular arrhythmia (disruption in the rhythm of the heart's lower chambers), which occurs in 84% of patients, long QT syndrome (recharging of the cardiac muscle is prolonged between heart beats), which has been reported to occur in 50% of patients, and bidirectional ventricular tachycardia (heart beat originating from alternate left and right ventricles), occurring in 32% of patients. If untreated, irregular heartbeats can lead to discomfort, fainting (syncope) or cardiac arrest (1). Some studies have demonstrated that men are less prone to develop ATS-associated cardiac events compared to women or adolescents (18, 25). It has been suggested that secondary mutations can exist in ATS, which augment repolarization reserves but reduce depolarization forces. A reduced sodium channel current due to an *SCN5a* loss-of-function mutation has been proposed to antagonize Q-T prolongation normally caused by reduction in IK_1, but aggravates arrhythmogenesis by reducing excitability and conduction (26).

In the majority of ATS patients there is also a prolonged terminal T wave downslope, a wide T–U wave and a biphasic and large U wave, all reflecting abnormalities in repolarization (9, 14, 27-29).

Neurocognitive deficits

A recent prospective study has identified deficits in neurocognition in ATS patients aged 8-45 years compared with their unaffected siblings. Although assessment of verbal or visual memory, EEGs and IQ scores were similar between the two groups, ATS patients reported more difficulties at school. Detailed neurocognitive testing showed that ATS patients had decreased scores on tests of executive functioning, matrix reasoning, mathematics and reading (30).

Treatment

There are limited data from randomized, controlled studies of potential therapeutics for ATS; to date, the majority of published investigations focus on case studies. Because of differences in cardiac and skeletal muscle physiology, drugs that may have a beneficial effect on cardiac function may have a detrimental effect on skeletal muscle, and *vice versa* (1).

A case report of a young woman with ATS (R218W mutation on the *KCNJ2* gene) observed that both amiodarone (an antiarrhythmic) and acetazolamide (a carbonic anhydrase inhibitor used to treat glaucoma, epileptic seizures and benign intracranial hypertension) can provide marked and long-lasting improvement of cardiac and muscular symptoms (31).

The favorable antiarrhythmic action of flecainide has also been demonstrated in a single case study of a young woman with ATS, demonstrating elimination of sustained bidirectional ventricular tachycardia over a 4-year period (32), as well as in a study of 2 siblings with ATS (33).

The calcium channel blocker verapamil has been shown to suppress ventricular arrhythmias symptomatic of ATS following oral administration in a case study conducted in a 65-year-old woman (34). Intravenous infusion has also yielded positive results in a case study of a 13-year-old girl (eliminating bidirectional ventricular tachycardia at a dose of 1 mg) (35) and in another case study conducted in an 18-year-old woman with ATS (2.5 mg) (36).

Finally, two multicenter, randomized, double-blind, placebo-controlled, crossover trials have demonstrated that dichlorphenamide (DCP, Daranide), a potent carbonic anhydrase inhibitor, can significantly reduce the rate of periodic paralysis attacks in patients with hypokalemia and in potassium-sensitive periodic paralysis patients (37), indicating that dichlorphenamide may be a potential therapeutic candidate for ATS.

References

1. Sansone, V., Tawil, R. *Management and treatment of Andersen-Tawil syndrome (ATS).* Neurotherapeutics 2007, 4(2): 233-7.

2. Donaldson, M.R., Yoon, G., Fu, Y.H., Ptacek, L.J. *Andersen-Tawil syndrome: A model of clinical variability, pleiotropy, and genetic heterogeneity.* Ann Med 2004, 36(Suppl. 1): 92-7.

3. Andersen, E.D., Krasilnikoff, P.A., Overvad, H. *Intermittent muscular weakness, extrasystoles, and multiple developmental anomalies. A new syndrome?* Acta Paediatr Scand 1971, 60(5): 559-64.

4. Plaster, N.M., Tawil, R., Tristani-Firouzi, M. et al. *Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome*. Cell 2001, 105(4): 511-9.

5. Lange, P.S., Er, F., Gassanov, N., Hoppe, U.C. *Andersen mutations of KCNJ2 suppress the native inward rectifier current IK1 in a dominant-negative fashion*. Cardiovasc Res 2003, 59(2): 321-7.

6. Nichols, C.G., Lopatin, A.N. *Inward rectifier potassium channels*. Annu Rev Physiol 1997, 59: 171-91.

7. Zobel, C., Cho, H.C., Nguyen, T.T. et al. *Molecular dissection of the inward rectifier potassium current (IK1) in rabbit cardiomyocytes: Evidence for heteromeric co-assembly of Kir2.1 and Kir2.2.* J Physiol 2003, 550(Pt. 2): 365-72.

8. Miake, J., Marban, E., Nuss, H.B. *Functional role of inward rectifier current in heart probed by Kir2.1 overexpression and dominant-negative suppression*. J Clin Invest 2003, 111(10): 1529-36.

9. Tristani-Firouzi, M., Jensen, J.L., Donaldson, M.R. et al. *Functional and clinical characterization of KCNJ2 mutations associated with LQT7 (Andersen syndrome).* J Clin Invest 2002, 110(3): 381-8.

10. Priori, S.G., Pandit, S.V., Rivolta, I. et al. *A novel form of short QT syndrome (SQT3) is caused by a mutation in the KCNJ2 gene.* Circ Res 2005, 96(7): 800-7.

11. Ballester, L.Y., Benson, D.W., Wong, B. et al. *Trafficking-competent and trafficking-defective KCNJ2 mutations in Andersen syndrome*. Hum Mutat 2006, 27(4): 388.

12. Bendahhou, S., Donaldson, M.R., Plaster, N.M., Tristani-Firouzi, M., Fu, Y.H., Ptacek, L.J. *Defective potassium channel Kir2.1 trafficking underlies Andersen-Tawil syndrome*. J Biol Chem 2003, 278(51): 51779-85.

13. Donaldson, M.R., Jensen, J.L., Tristani-Firouzi, M. et al. *PIP2 binding residues of Kir2.1 are common targets of mutations causing Andersen syndrome.* Neurology 2003, 60(11): 1811-6.

14. Seemann, G., Sachse, F.B., Weiss, D.L., Ptacek, L.J., Tristani-Firouzi, M. *Modeling of IK1 mutations in human left ventricular myocytes and tissue.* Am J Physiol Heart Circ Physiol 2007, 292(1): H549-59.

15. Tawil, R., Ptacek, L.J., Pavlakis, S.G. et al. *Andersen's syndrome: Potassium-sensitive periodic paralysis, ventricular ectopy, and dysmorphic features*. Ann Neurol 1994, 35(3): 326-30.

16. Preisig-Muller, R., Schlichthorl, G., Goerge, T. et al. *Heteromerization of Kir2.x potassium channels contributes to the phenotype of Andersen's syndrome*. Proc Natl Acad Sci USA 2002, 99(11): 7774-9.

17. *Characteristics of Andersen-Tawil syndrome (NCT00521794).* ClinicalTrials.gov Web site, July 22, 2008.

18. Andelfinger, G., Tapper, A.R., Welch, R.C., Vanoye, C.G., George, A.L. Jr., Benson, D.W. *KCNJ2 mutation results in Andersen syndrome with sex-specific cardiac and skeletal muscle phenotypes.* Am J Hum Genet 2002, 71(3): 663-8.

19. Canun, S., Perez, N., Beirana, L.G. *Andersen syndrome autosomal dominant in three generations.* Am J Med Genet 1999, 85(2): 147-56.

20. Yoon, G., Oberoi, S., Tristani-Firouzi, M. et al. *Andersen-Tawil syndrome: Prospective cohort analysis and expansion of the phenotype*. Am J Med Genet A 2006, 140(4): 312-21.

21. Sansone, V., Griggs, R.C., Meola, G. et al. *Andersen's syndrome: A distinct periodic paralysis.* Ann Neurol 1997, 42(3): 305-12.

22. Venance, S.L., Cannon, S.C., Fialho, D. et al. *The primary periodic paralyses: Diagnosis, pathogenesis and treatment*. Brain 2006, 129(Pt. 1): 8-17.

23. McManis, P.G., Lambert, E.H., Daube, J.R. *The exercise test in periodic paralysis*. Muscle Nerve 1986, 9(8): 704-10.

24. Katz, J.S., Wolfe, G.I., Iannaccone, S., Bryan, W.W., Barohn, R.J. *The exercise test in Andersen syndrome*. Arch Neurol 1999, 56(3): 352-6.

25. Khan, I.A. *Long QT syndrome: Diagnosis and management*. Am Heart J 2002, 143(1): 7-14.

26. Pollevick, G.D., Buerchicoff, A., Carrier, T., Kanter, R.J., Antzelevitch, C. *Compound heterozygous mutations in KCNJ2 and SCN5A associated with life-threatening ventricular tachycardia in the absence of long QT or clinical manifestations of Andersen-Tawil syndrome.* 28th Annu Sci Sess Heart Rhythm Soc (NASPE) (May 9-12, Denver) 2007, Abst PO2-128.

27. Morita, H., Zipes, D.P., Morita, S.T., Wu, J. *Mechanism of U wave and polymorphic ventricular tachycardia in a canine tissue model of Andersen-Tawil syndrome*. Cardiovasc Res 2007, 75(3): 510-8.

28. Garcia-Touchard, A., Somers, V.K., Kara, T. et al. *Ventricular ectopy during REM sleep: Implications for nocturnal sudden cardiac death.* Nat Clin Pract Cardiovasc Med 2007, 4(5): 284-8.

29. Zhang, L., Benson, D.W., Tristani-Firouzi, M. et al. *Electrocardiographic features in Andersen-Tawil syndrome patients with KCNJ2 mutations: Characteristic T-U-wave patterns predict the KCNJ2 genotype.* Circulation 2005, 111(21): 2720-6.

30. Yoon, G., Quitania, L., Kramer, J.H., Fu, Y.H., Miller, B.L., Ptacek, L.J. *Andersen-Tawil syndrome: Definition of a neurocognitive phenotype.* Neurology 2006, 66(11): 1703-10.

31. Junker, J., Haverkamp, W., Schulze-Bahr, E., Eckardt, L., Paulus, W., Kiefer, R. *Amiodarone and acetazolamide for the treatment of genetically confirmed severe Andersen syndrome*. Neurology 2002, 59(3): 466.

32. Pellizzon, O.A., Kalaizich, L., Ptacek, L.J., Tristani-Firouzi, M., Gonzalez, M.D. *Flecainide suppresses bidirectional ventricular tachycardia and reverses tachycardia-induced cardiomyopathy in Andersen-Tawil syndrome*. J Cardiovasc Electrophysiol 2008, 19(1): 95-7.

33. Bokenkamp, R., Wilde, A.A., Schalij, M.J., Blom, N.A. *Flecainide for recurrent malignant ventricular arrhythmias in two*

siblings with Andersen-Tawil syndrome. Heart Rhythm 2007, 4(4): 508-11.

34. Erdogan, O., Aksoy, A., Turgut, N., Durusoy, E., Samsa, M., Altun, A. *Oral verapamil effectively suppressed complex ventricular arrhythmias and unmasked U waves in a patient with Andersen-Tawil syndrome.* J Electrocardiol 2008, 41(4): 325-8.

35. Sumitomo, N., Shimizu, W., Taniguchi, K., Hiraoka, M. *Calcium channel blocker and adenosine triphosphate terminate bidirectional ventricular tachycardia in a patient with Andersen-Tawil syndrome*. Heart Rhythm 2008, 5(3): 498-9.

36. Kannankeril, P.J., Roden, D.M., Fish, F.A. *Suppression of bidirectional ventricular tachycardia and unmasking of prolonged QT interval with verapamil in Andersen's syndrome*. J Cardiovasc Electrophysiol 2004, 15(1): 119.

37. Tawil, R., McDermott, M.P., Brown, R. Jr. et al. *Randomized trials of dichlorphenamide in the periodic paralyses. Working Group on Periodic Paralysis.* Ann Neurol 2000, 47(1): 46-53.