REVIEW

Andersen Syndrome: The Newest Variant of the Hereditary-Familial Long QT Syndrome

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Andersen's Syndrome is a rare disease, hereditary with autosomal dominant transmission, of the ion channels of the sarcolemmal membranes of the cardiac and skeletal muscles (channelopathy), which affects chromosome 17 of the KCNJ2 gene, responsible for encoding the outward potassium delayed rectifier current KIR2.1, resulting in a loss or suppression of the function of this channel.

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Andersen's Syndrome (AS)¹ is a rare channelopathy that affects the excitability of cardiac and skeletal muscle membranes, characterized by potassium-sensitive periodic paralysis, ECG with long QT interval and tendency to arrhythmias; bone structure deformities, hereditary with autosomal dominant transmission caused by mutations in the locus of chromosome 17q23 of the gene KCNJ2, which is responsible for encoding the outward potassium rectifier current Kir2.1.¹ This is the main channel responsible for the characteristics of resting transmembrane potential (RTP), with an important role in excitability control of skeletal and cardiac muscle fibers.²

Channelopathy is the term used to describe disorders causing defects in the proteins that make up the structure of the ionic channels in the sarcolemma and intracellular membranes.

The finding that AS is a channel disease presents important lessons for the field of human channelopathies. This is a first example in which a channel defect concomitantly causes alterations in voluntary and cardiac muscles and bone development.

The channel Kir2.1 is part of a large family of channels of K⁺ that help in cation outflow regulation in muscle cells. The K⁺ channels have an essential role in the generation of electric activity of certain cell types. In the heart, they act in phase 3 of transmembrane action potential (TAP), which corresponds to the ventricles in surface ECG, to the T wave of ventricular repolarization and in the atria to the Ta or Tp waves. Together with phase 2, it corresponds to the cardiac cycle to the ejection period, i.e., when the aortic and pulmonary sigmoid valves are open.

AS is characterized by the following:

1. Potassium-sensitive periodic paralysis;
2. Long QT interval with a tendency to arrhythmia;
3. Deformities in bone structure;
4. Proximal muscle atrophy without myotonic disorders.

Andersen et al. presented for the first time in 1971, an 8-year-old child, who was a carrier of a different syndrome, characterized by the association

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¹Andersen's syndrome must not be confused with the so-called Andersen's disease type IV: this being a glycogen storage entity. It is a liver glycogenosis by deficiency of the enzyme 1.4 to 1.6 transglycosylase (branching enzyme). The liver is the main organ involved, resulting in a glycogenolysis defect.

of intermittent muscle weakness, extrasystoles, and multiple development anomalies,³ corresponding to what is now known as AS.

Potassium-Sensitive Periodic Paralysis

The level of serum K^+ during the episode of paralysis is usually normal or slightly low; however, spontaneous paralytic attacks can be associated to hypo, normo, or hyperpotassemia.

This entity cannot be grouped within the classification of periodic paralysis based on serum K^+ concentration.⁴ Thus it is differentiated from hyperkalemic periodic paralysis, also mapped in chromosome 17 by mutation of the gene of the Na^+ channel of the skeletal muscle in the alpha subunit of the gene SCN4A, and from the hypokalemic periodic paralysis mapped in chromosome 1q31-32 and related to the mutation in the alpha subunit of the calcium channel sensitive to dihydropyridine (CACNL1A3).⁵

Long QT Interval

It is seen to be associated with a tendency to ventricular ectopies, such as bigeminal ventricular extrasystoles, multifocal ventricular tachycardias (VT), and bidirectional VT, both originated by the electrophysiologic mechanism of these arrhythmias is due to a 'triggered activity' by delayed afterdepolarizations (DAPs) in phase 4.

In every patient with periodic paralysis clinics, cardiac evaluation must be carried out with serial ECGs, with the aim of making a sequential medication of QT interval. The latter, when extended, is a fundamental feature of AS and can be the only element existing.⁶

The test of tolerance to glucose worsens dysrhythmias; on the contrary, the test of tolerance to glucose worsens dysrhythmias and the administration of acetazolamide prevents periodic muscular paralysis occurrence. Ventricular ectopies seem to worsen with decrease of serum K^+ levels and improve with its increase.

Cardiac arrest has been reported in some individuals.

There are reports of cardiovascular malformations, such as isolated bicuspid aortic valve, associated with aorta coarctation, or pulmonary valve stenosis. Unilateral renal dysplasia has been reported as well.⁷

AS is characterized by anomalies in bone development or deformities in the bone structure (dysmorphic characteristics): wormian bones, short stature, scoliosis, strange-looking face characterized by a broad forehead, low set ears, broad nasal root, malar and mandible hypoplasia (micrognathia), high arched palate by defect in the soft and hard palate (cleft palate), hypertelorism, and ptosis of eyelids.

Cranial deformities include macrocephaly, scaphocephaly, and undermineralization of skull.

Limb deformities include brachydactyly, syndactyly, clinodactyly, and tapering fingers, and muscle atrophy secondary to myopathy with muscle weakness and without myotonia.

Not all the affected individuals present all of the manifestations, and in half of the cases, the diagnosis is made after several evaluations, and only when the dysmorphic alterations are recognized.

AS considered today is variant 7 of the long QT syndrome or SQT7. In Table 1, the seven known genetic variants of LQTS are presented with their main features.

ETIOLOGY

AS is caused by mutations in the gene KCNJ2, responsible for the internal encoding of the potassium rectifier current Kir2.1 of the heart and the skeletal muscle. All the mutations found in AS result in a loss or suppression of the Kir2.1 current function. This current is responsible for the balanced state of the diastolic or resting transmembrane potential (DTP or RTP) E_1 or E_x called I_{K1} , "inward rectifier," Kir or IRK1 (K^+ Inward Rectifier). The current Kir2.1 belongs to a subfamily of channels called Kir2.x, with the following types identified: Kir2.3, Kir2.2, and Kir2.1. The channel has its effect in the final part of phase 3 of TAP and causes outflow of K^+ in the hyperpolarized state, thus preventing the excessive loss of intracellular cations in the cases with prolonged phase 2. It has two domains called M1 and M2 and a single pore or P loop with a carboxyl (C) group and another N-terminal amino acid. The carboxyl is the element that defines the properties of the channel. In the M2 domain of the subvariety Kir2.1 the aspartic amino acids 172 and glutamic amino acid 224 were identified as being the locations of the channel filtering. Additionally, there are two extracellular loops, E1 and E2, separated by a segment that constitutes the intramembrane pore called H5. This H5 segment

Table 1. Genetic variants of hereditary-familial LQTS

Gene	Name	Locus	Mutation	Affected Channel	Affected Phase of Transmembrane Action Potential (TAP) and Arrhythmia Triggers
LQTS1 KV-LQT1 KCNQ1 60% of cases. KCNQ1	KVLQT1 It can cause both the Romano-Ward syndrome and the Jervell and Lange-Nielsen syndrome.	Chromosome 11	11p15.5 OMIM NO: 192500	I_{Ks} : Outward potassium delayed rectifier current.	Phase: 3 Trigger: stress.
LQTS2 35% of cases. KCNH2	HERG: THE HUMAN ETHER-A-GO-GO	Chromosome 7	7p35-36 OMIM NO: 152.427	I_{Kr} Outward potassium fast rectifier current:	Phase: 2, plateau or dome. Trigger: unexpected noise.
LQTS3 1% of cases.	SCN5A alpha subunit.	Chromosome 3	3p 21-24 OMIM NO *: 600163. NO = number	I_{Na+} Sodium current.	Phase 0 and 2 Trigger: sleep and vagotony. It is an allelic entity to Brugada disease.
LQTS4	?	Chromosome 4	4q 25-q27 OMIM NO: 600919	?	Variants of this gene were found in a large family with LQTS. The precise location of the gene is still unknown. Genes receive a name once their estimated location is known.
LQTS5 KCNE2	Mink	Chromosome 21	21q22.1 OMIM NO: 603796	I_{Ks} Outward potassium delayed rectifier current.	Phase 3. Associated to Jervell and Lange-Nielsen syndrome with congenital sensorineural deafness.
LQTS6	KCNE2 GLN9GLU MET54THR ILE57THR	Chromosome 21	21q22.21 21q22.1-q22.2	I_{Kr} Outward potassium fast rectifier current.	Phase 2 Trigger: certain drugs and exercises.
LQTS7	KCNJ2	Chromosome 17			Associated with Andersen's syndrome.

*OMIM NO: it refers to the entry number of the locus at <http://www.ncbi.nlm.nih.gov/htbin-post/Omim>.

contains eight large residues similar to the voltage-dependent K^+ currents. This stretch is called "K⁺ current signature sequence".⁸

The pore can have more than one concomitant blocking point, being blocked by the cations Mg^{2+} and Ca^{2+} in hyperpolarization states. Consequently, channel I_{K1} is blocked in a voltage-dependent fashion by intracellular Mg^{2+} and by intracellular polyamines, and modulated by prolonged repolarization. The identified polyamines are spermine, spermidine, and putrescine. There seems to be more than one blocking point of Mg^{2+}

and polyamines. The blocking power of spermine for the I_{K1} current is four times higher than Mg^{2+} due to its great affinity with the current.

When the potential of the membrane is discretely depolarized, the spermine block substitutes the Mg^{2+} block decreasing the number of channels that can reopen.

The channel performance is independent of voltage. In the cases where intracellular pH is increased, there is accelerated inactivation of the I_{K1} channel, pointing towards the existence of an intrinsic regulation mechanism.

The channel is activated by anionic phospholipids, phospho-inositol 4-5-biphosphate with no need of ATP by electrostatic interaction with a terminal carboxyl group that keep it open.

In AS several mutations were described:

- Missense, heterozygotic, mutation (R67W):
- Missense mutation in gene KCNJ2 (conversion D71V) identified in a family group;
- Missense mutation in gene KCNJ2, Thr192Ala (T192A), identified in the second M2 transmembrane region⁹ located in cytoplasm, specifically in the sarcoplasmic reticulum of the K⁺ or Kirs current.

Additionally, another eight mutations were identified in several patients.

Studies made on *Xenopus* oocytes reveal a loss of function and a dominant negative effect in the rectifier Kir2.1 current, while voltage increases.

The allele mutant to the Kir2.1 current has a tetrameric differentiation with wild-type channels like Kir2.1, Kir2.2, and Kir2.3, which represent the molecular basis for the extraordinary pleiomorphism of AS.¹⁰

The analysis of these mutations revealed that there is a critical alteration in the segments of the Kir2.1 current, including the pore region—through which the potassium goes through—and in other regions.

Even though arrhythmias are frequent, in AS there is no significant tendency to sudden death; nevertheless, it is not impossible, since there have already been reports of syncope and sudden death itself.

Reduction of potassium rectifier currents Kir2.1 extends the final phase of TAP, and in the situation of hypopotassemia, they induce the so-called Na⁺/Ca²⁺ exchange current or I_{Na⁺-Ca²⁺} exchange current (this channel exchanges three molecules of Na⁺ with one of Ca²⁺), bringing about the appearance of delayed afterdepolarization, and consequently, induction to arrhythmias. These facts suggest that the substrate of higher susceptibility for arrhythmias found in AS is different than other forms of hereditary LQTS.¹¹

The *exercise stress test* in AS can confirm the diagnosis of periodic paralysis.

In AS a progressive decrease was observed in muscle TAP width after efforts, which constitutes a characteristic phenomenon of periodic paralysis.

An improvement in the duration of attacks and a reduction in their number and in muscle weakness occurs with the test.

The exercise stress test was used to confirm the diagnosis of periodic paralysis in AS and to assess the neuromuscular state.¹²

TREATMENT

It remains empirical and occasionally frustrating due to the eventual paradoxical response by both the skeletal and cardiac muscles to the exchange of serum K⁺.

The use of carbonic anhydrase inhibitors, such as nonbacteriostatic sulphonamide acetazolamide (diamox^R), causes mild metabolic acidosis, and they are considered better than thiazide diuretics for control of periodic weaknesses, since they do not cause unwanted hypopotassemia.

Dosage

Although some patients respond to low doses, the optimal range seems to be from 500 mg to 1000 mg/day. Acetazolamide (250 mg), thrice a day is the recommended mean (8–30 mg/kg) in doses distributed each 8 hours.

Presentation: 250 mg tablets.

Unwanted Effects

Death occurred, although very rarely, due to severe reactions to sulphonamide, including the Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood discrasias. Sensitization can happen again when a sulphonamide is administered once more, regardless the via of administration. If there are signs of hypersensitivity or other severe signs, the use of this drug must be interrupted.

When acetazolamide is used in association with amiodarone, there is an improvement in cardiac and muscle symptoms.

In this syndrome the arrhythmias are more difficult to treat, because there is a loss of response to drugs, plus a worsening of the skeletal muscle function.

CONCLUSIONS

AS is a rare autosomal dominant hereditary channelopathy, which affects chromosome 17 in

the gene KCNJ2, responsible for the Kir2.1 rectifier current encoding, and the main channel responsible for the features of the resting transmembrane potential.

During hypokalaemia the reduction of these channels extends the final phase of TAP and fosters the $\text{Na}^+/\text{Ca}^{2+}$ exchange current to function, thus bringing about the appearance of delayed after-depolarization and induction to arrhythmias.

Currently it is considered as variant 7 of the hereditary familial LQTS syndrome.

Clinically, the diagnosis is made in the presence of concomitant potassium-sensitive periodic paralysis, prolonged QT interval, and tendency to ventricular arrhythmias, rarely lethal.

All patients with periodic paralysis should undergo serial ECGs to make a sequential medication of the QT interval.

The phenotype can present characteristic skeleton deformities, as short stature, scoliosis, macrocephaly, face with a broad forehead, ptosis of eyelids, low set ears, broad nasal root, cleft palate, micrognathia, brachydactyly, syndactyly, clinodactyly, and tapering fingers, and proximal muscle atrophy without myotonia.

The exercise stress test is useful to confirm the diagnosis and to assess the neuromuscular state.

The treatment is empirical and with variable results. Acetazolamide can be employed in isolation or associated to amiodarone.

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