Cardiac Channelopathies

With the title **"Cardiac Channelopathies",** published in Nature Vol 415, 10 January 2002, Dr. Eduardo Marban explores the pathophysiology of ionic channels, this being a text that must be read obligatorily to understand the events that happen in syndromes such as the one we are dealing with, and in other entities where such channels have been affected.
Considering its relevance, the mentioned text is included as part of the list of topics for this First Virtual Symposium about the Brugada Syndrome, for which we have the authorization by Dr. Marban and the editors of Nature.
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The following material is an introduction of which we are authors, that we dared to write for Dr. Marban's paper.

DISORDERS OF MEMBRANE CHANNELS OR CHANNELOPATHIES AND ITS RELATIONSHIP WITH THE BRUGADA DISEASE

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Brugada Disease (BrD) is a distinct subgroup of patient's form of idiopathic ventricular fibrillation (IVF). It is occasinated by a mutation in a cardiac Na^+ channel gene, SCN5A, localized in the number three chromosome, has been linked to BrD, which cause the Na^+ channel to badfunction, and is worsened by Na-channel blocking agents. The channels affected in BrD are: primarily the rapid sodium channel and secondarily the " transient outward K^+ current", "4 aminopyridine sensitive outward current", or I_{to} channel and L-type (slow or long-lasting) calcium channel $I_{Ca\text{-}L\ type}$ $I_{Ca^{++}\text{-}L}$ **(1).**
There are many diseases related to ion channels: the "channelopathies" or ions related channels diseases that can to affect: sodium, potassium, (I_{to} or transient outward current and delayed rectifier current (I_{ks} I_{ks} I_{kur}),,) chloride, calcium, and acetylcholine-gated channels. Its entities may lead to such physiological disorders affecting the cardiovascular, neurological, oftalmological, psiquatric, and others systems as those stated bellow **(2)**

A) Cardiovascular entities related with channels diseases:

Is now understood to be a collection of genetically distinct arrhythmogenic cardiovascular disorders resulting from mutations in fundamental cardiac ion channels that orchestrate the transmembrane action potential (TAP) of the human heart.
The more important channelopaties that affect the cardiovascular system are:

1) Long QT syndromes (LQTS): More than 35 mutations in four cardiac ion channel genes--KVLQT1 (voltage-gated K channel gene causing one of the autosomal dominant forms of LQTS) (LQT1), HERG (human ether-a-go-go related gene.) (LQT2), SCN5A (LQT3), and KCNE1 (minK, LQT5)--have been identified in LQTS. Five genes have been implicated in the Romano-Ward syndrome, the autosomal dominant form of LQTS: KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. Mutations in KVLQT1 and KCNE1 also cause the Jervell and Lange-Nielsen syndrome, a form of LQTS associated with deafness, a phenotypic abnormality inherited in an autosomal recessive fashion. These genes encode ion channels responsible for three of the fundamental ionic currents in the cardiac TAP. In the LQTS several mutations have been identified both in the sodium and in the potassium channels. The different electrophysiological effects of the mutations lead to a common phenotype: prolongation of the QT interval; but also to a common clinical impact: occurrence of malignant ventricular arrhythmias(3) LQTS are cardiovascular disorders characterized by prolongation of the QT interval on ECG associated to tendency of syncope, seizures, and sudden cardiac death.

The table 1 below show its aspect

Table 1

Disease Autosomal dominant	**Autosomal recessive**	***Channel affected***	***Gene***	**Effect of mutation**	**Chromosome**
LQT1	**JLN1**	**I_{ks}**	**KVLQT1**	**< function**	**11p15.5**
LQT2		**I_{kr}**	***HERG***	**< function**	**7q35-36**
LQT3		**I_{Na}^{+}**	***SCN5A***	**> function**	**3p21-24**
LQT4		**?**	***?***	**?**	**4q 25-27**
LQT5	**JLN2**	**I_{ks}**	***MinK***	**< function**	**21q22**

Genes responsible for LQT1, LQT2, have been identified as cardiac potassium channel genes (KVLQT1, HERG) genes (KVLQT1, HERG).
Genes responsible for LQT3 have been identified in the cardiac sodium channel gene (SCN5A**).**

2) Brugada disease: is a distinct form of so-called idiopathic ventricular fibrillation (IVF) in which patients are characterized by J point and ST segment elevation in the right precordial leads of electrocardiogram with a normal QTc, in men. It is an inherited cardiac disease that causes sudden death related to idiopathic ventricular fibrillation in a structurally normal heart. Linked to autosomal dominant mutations in SCN5A, the gene encoding the human cardiac Na(+) (channel sodium channelopathy.). Three kinds of mutations have been described in the SNC5A, known as missence mutation, splice-donor mutation and frame shift mutation (4) The missence mutation is responsible for the quick recovery of Na^{+} channels from inactivation, while the frame mutation determines the channel inactivation, with the subsequent heterogeneous leveling of phase 2 in the right ventricle epicardium (precisely those in front of ECG derivations V1 to V3) but not in the endocardium. The I_{to} channel of phase 1, in the epicardium is more evident (due to an increase in K^{+} outlet) conducing an accentuated dispersion of ventricular repolarization and refractory period, which constitutes an ideal substrate for the development of fuctional reentrant arrhythmia. Because the I_{to} channel becomes less

prominent at a faster rate, increased heart rate is associated with decreased of J point and ST segment elevation on ECG and probably decreased incidence of PVT **(5).**

The channel I_{to} alteration and ICa^{2+}-L are the electrophysiologic substrate explaining the persistent point J elevation and the ST elevation in this entity, and the precocius repolarization by a small loss in phase 1 (nochet) and 2 (plateau or dome) in the epicardium and not in the endocardium of the same ventricular mass **(6).** In phase 1 a rapid repolarization of APT coincide with the point J of surface ECG, we verify a still small Na^+ income in decline and slow beginning of K^+ outcome "in crescendo", through the hole of the so called I_{to} channel. This channel has two varieties, one activated by voltage amplitude and modulated by neurotransmitter, and the other by the amount of intracellular Ca^{++}, known as I_{to2}. There are different densities of I_{to} channels in the width of ventricular myocardium, a greater amount in the epicardium and lower or absent in the endocardium. This uneven density is responsible for the fact that the nochet of fase 1, is deeper in the epicardium and shallower or absent in the endocardium **(7).**

The idiopathic polymorphic ventricular tachycardia of the BrD is not provoked by exertion differently of IPVT with a normal QT interval verapamil sensitive, torsade de pointes (TdP) with LQTS and catecholaminergic polymorphic ventricular tachycardia. The IPVT in the BrD may be triggered by fever, anti-malaric agents, antidepressants (particularly excessive doses of three-cycle ones), anti-arrhythmic agents class IA (ajmaline and procainamide) and IC (flecainide, propafenone and pilsicainide), hyperglycemia, bradycardia and alcohol consumption. The Brugada syndrome is masked during exercise and it becomes apparent in the post-effort phase. The I_{to} channel during high cardiac frequencies becomes less prominent, which explains the decrease in ST segment elevation and of incidence of IPVT in higher frequencies. This fact is a basis for indicating overdrive pacing in prevention of IVF in the BrD **(8).**

3) LQT3 variant from of LQTS: It is considered the mirror image of the BrD. Identification of autosomal dominant mutations in the cardiac sodium channel gene SCN5A of Chromosome 3p21-p24; . The site of mutation is different and result in a prolonged QT interval with late initiation of T wave and long QT interval. Cardiac Na+ channel a subunit; SCN5A .

Cardiac clinical events

- Syncope, Aborted cardiac arrest, Sudden cardiac death
- Frequency of cardiac events with mutation: 18%
- Risk of death from cardiac event: 20%
- Cardiac events less frequent but more likely lethal than LQT1 or LQT2
- Allelic Mutations also produce: Idiopathic ventricular fibrillation and BrD.

4) Idiopathic ventricular fibrillation (IVF): IVF may occur in about 1 per cent of cases of out-of-Hospital VF affects mostly men and those in middle age. Some Ventricular fibrillation leading to sudden cardiac death in the absence of structural heart disease without ST segment elevation in the right precordial leads of electrocardiogram spontaneously or drug induced. It is a sodium channelopathy with identification of mutation in the cardiac sodium channel on gene SCN5A Two mutations associated with IVF are localized within extracellular loops between segments DIIIS1-S2 (R1232W) and DIVS3-S4 (T1620M) of the human cardiac sodium channel (hNav1.5) alpha-subunit**(9-10).**

5) Lenègre "idiopathic" progressive disease of His-Purkinje system: Progressive cardiac conduction defect (PCCD), also called Lenègre-Lev disease (11) is one of the most common cardiac conduction disturbances. It is characterized by progressive alteration of cardiac conduction through the His-Purkinje system with right or left bundle branch block and widening of QRS complexes, leading to complete atrioventricular block and causing syncope and sudden death. It represents the

major cause of pacemaker implantation in the world (0.15 implantation per 1,000 inhabitants per year in developed countries). Of unknown origin, PCCD is considered a primary degenerative disease or an exaggerated aging process with sclerosis affecting only the conduction tissue. Familial cases with right bundle branch block have been reported. One locus, designated HB1, maps to 19q13.3. Lev's and Lenegre's disease are pathologic diagnoses; both involve idiopathic fibrosis of the conducting system. Since they are pathologic diagnoses, I do not know if they can be distinguished clinically, although Lenegre's disease is said to affect younger patients. Lev's and Lenegre's disease can be due to fibrosis of the conduction system in individuals less than 40 years of age (Lenegre's disease) while in older individuals it is known as Lev's disease.

Mobitz 2 2nd degree A-V block at the level of the AV node is not uncommon during sleep in young patients, generally due to hypervagotonia. Infranodal block during sleep is not physiologic.

The PCCD many cause left bundle branch block or right bundle branch block associate with and Left Antero-Superior Divisional Block, (LASDB) Left posterior -inferior divisional block (LPIDB) , and antero-medial divisional block (AMDB)

. The left bundle is a large robust structure on the left side of the septum that divides into and anterior, middle and posterior fascicles. Conduction can be blocked or slowed by ischemia or infarction, often associated with left ventricular hypertrophy and/or dilation, aortic ou mitral valve disease, Progressive cardiac conduction defect (PCCD) and others causes as shown in the following list below:

Possible etiologies for advanced left bundle branch block

Relationship of the causes quoted in literature:

1- Systemic arterial hypertension (SAH): main isolated or associated cause.
2- Coronary insufficiency (CI): controversial: 20 to 70% of cases.
3- Association of SAH and CI: 70% of cases.
4- Cardiomyopathies.
5- Post-surgery in myotomy/miectomy (septectomy) in hypertrophic cardiomyopathy.
6- Aortic-valve disease
7- Mitral valve disease
8- Progressive cardiac conduction defect (PCCD):
   a) Sclerosis of the left side of the cardiac skeleton: Lev disease
   b) Progressive “idiopathic” sclerosis of the His-Purkinje conduction system: Lenégre disease
9- Miscellaneous causes secondary to:
   10- congenital heart diseases
   11- cardioplegia with blood or crystalloid (Gundry et al)
   12- use of taxol, anti-neoplasmic cytotoxic agent (Rowinsky et al)
   13- primary amyloidosis
   14- sarcoidosis
   15- hyperkalemia
   16- without apparent cause

In these Lenègre patients, the survival depends more on the extension of the lesion, and it could eventually need of a pacemaker in symptomatic cases to avoid SCD by progression of complete LBBB.

Cardiac conduction defect and familial sudden death have been demonstrated to have various genetic and nongenetic causes. Green et al **(12)** described a family in which sudden death occurred in at least 10 persons in 3 generations at an average age of 21 years (range 4-44). No clinical abnormalities were detectable in members of the family, including one who died suddenly. An abnormality of the conduction system was postulated but not definitely demonstrated.

Gault, J. et al **(13)** described a 10-year-old girl with alternating bidirection tachycardia. Autopsy showed fatty and mononuclear cell infiltration in the atrioventricular conduction system and the main left bundle branch. A similar arrhythmia was documented in an 18-year-old sister. Autopsy showed no gross cardiac abnormality but the conduction system was not studied. A brother, aged 21 years, and the mother, aged 45, also had ventricular bigeminal rhythm and the maternal grandmother and a maternal uncle had died suddenly. Cardiac irregularity was known to have been present in the grandmother.

Lynch et at.**(14)** described a kindred in which many persons in several generations had a progressive atrioventricular conduction defect. Prolonged AV conduction had its onset usually in the 30s with loss of R waves in the right precordial leads. Arrhythmia occurred only as a late manifestation. Syncopal attacks were the main symptom. Progression from first- to third-degree block was usually slow, but in a few persons a relatively fulminate course with death in 2 or 3 years was observed. Since the disorder appears to be limited to the conduction system, prognosis with artificial pacemaker should be excellent. The authors found several reports that may concern the same disorder.

Brookfield et al. **(15)** reported a case of a 15.5-year-old boy died suddenly after completing a 100-yard swim. He had had 4 syncopal episodes over a 3-year period, all occurring after strenuous exercise; extensive studies, including cardiac catheterization and electrophysiologic studies, revealed no abnormality. The patient's 12-year-old brother had died suddenly while swimming about 16 months before the proband's death. A maternal uncle had died at age 18, and 2 brothers of the maternal grandfather had died at ages 17 and 15. The great grandmother had died at age 35. All of these were sudden deaths. The mother and the maternal grandfather, presumed carriers, were normal by physical examination, electrocardiogram, and 2D echocardiogram, except for induction of ventricular ectopic beats and polymorphic nonsustained (325 beats) ventricular tachycardia with some procedures. The patient had been placed on 40 mg of nadolol, a beta-adrenergic blocker, 1 year before death. Also, the patient developed right bundle branch block after infusion of isoproterenol. Autopsy showed right ventricular septal hypertrophy with displacement of the conduction bundle. Thus, this family may fall in the category of asymmetric septal hypertrophy.

Strasberg et al **(16)** described a mother and daughter with paroxysmal torsade de pointes. Both had structural normal hearts and a normal QT interval. Both were successfully treated wtih propranolol during their limited follow up.

Chambers et al **(17)** described familial sudden death syndrome with an abnormal signal-averaged electrocardiogram. raised the question of whether an abnormal signal-averaged electrocardiogram may be a marker for the sudden death trait.

In an extensively affected French family Schott et al. **(18)** showed that progressive conduction defect was due to mutation in the SCN5A gene . In a smaller Dutch family, another SCN5A mutation was found to be associated with congenital nonprogressive conduction defect. Thus, the conduction defect caused by mutation in the SCN5A gene is not always progressive.

Identification of mutation that causes a sustained, isolated conduction defect with pathological slowing of the cardiac rhythm in the cardiac sodium channel gene SCN5A. This mutation results in the substitution of cysteine 514 for glycine (G514C) in the channel protein **(19-20).**
Biophysical characterization of the mutant channel shows that there are abnormalities in voltage-dependent 'gating' behaviour that can be partially corrected by dexamethasone, consistent with the salutary effects of glucocorticoids on the clinical phenotype **(21).** Computational analysis predicts that the gating defects of G514C selectively slow myocardial conduction, but do not provoke the rapid cardiac arrhythmias associated previously with SCN5A mutations. A recent publication tells about the discovery of two new heterozygotic allelic mutations in Brugada syndrome, located in the alpha subunit of the sodium channel in the SCN5A gene, which is clinically translated into AV block. These

two mutations are the result of the substitution of the serine amino acid by glycine (G298S) in the dominion of the I S5-S6 loop, and of asparagine for aspartic acid within the S3 of the IV dominion (D1595N). Both mutations cause:

1) obstruction for fast inactivation

2) reduction of density in sodium channels

3) increased slow component of inactivation

This combination of facts slows down the conduction and leads to AV block **(22).**
Recently, Japanese investigators studied an IVF mutation (S1710L) that exhibited an unusual clinical phenotype: rate-dependent bundle branch block without manifestation of Brugada-type ECG pattern. The functional abnormalities caused by S1710L mutation may be responsible for the overlapping clinical phenotypes associated with Brugada syndrome and the cardiac conduction defect, a novel cardiac Na(+) channelopathy. The mutant S1710L channels were expressed in mammalian cells and their gating properties, studied using whole-cell patch clamp techniques, were compared with wild-type (WT) and a Brugada syndrome mutant channel T1620M. The S1710L channel exhibited significantly faster macroscopic current decay than WT or T1620M. In addition, S1710L showed a negative shift in the voltage-dependence of fast inactivation and slower recovery from fast inactivation than in WT or T1620M. In addition to the alterations in fast inactivation most commonly observed in Brugada syndrome mutations, S1710L exhibited marked enhancement in slow inactivation and a large positive shift of activation that potentially decreases conduction velocity **(23).**

6) Mix forms of Brugada syndrome and LQT3 variant: QTc prolonged associated with atipical right bundle-branch block (RBBB) or right ventricular conduction delay, J point and ST segment elevation principally convex toward the top in the right precordial leads, (idiopatic J wave). Identification of mutation in the cardiac sodium channel gene SCN5A **(24-25).**

7) The Sudden Unexpected Nocturnal Death Syndrome (SUNDS): Recent identification of mutation in the cardiac sodium channel gene SCN5A **(26)** showed that SUNDS and BrD are the same entity. Death occurred within minutes after the onset of agonal respiration. A few patients who were successfully resuscitated were found to have VF and inducible IPVT/IVF in the electrophysiology laboratory. It is worth noting that the natives in Asia have known about the problem for many decades.
In the Philippines it is known as bangungut ("scream followed by sudden death during sleep") In Japan as pokkuri ("unexpected sudden death at night").In Thailand, this form of death is lai-tai ("death during sleep"). Thailand believe that the young men died during sleep because widow ghosts came to take them away. Many young men actually dressed as women go to sleep at night -a practice carried out for more than 70 years in the hope that it would mislead the widow ghosts who then would not take these young men. Unexpected SCD is the most common cause of natural death in young Thai men. It has only recently been discovered that these patients suffer the BrD.
The SUNDS is known to mainly affect utterly healthy young men between the ages of 22 and 45. Many of the victims had no history of heart trouble, yet they died of a heart attack.

8) Sudden infant death syndrome:
The sudden death of an infant under 1 year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history **(27)** A recent publication reported that a significant number of SIDS cases

in Italy had prolongation of the QT interval on a screening electrocardiogram, which may have led to a fatal cardiac arrhythmia **(28)** However, questions about the study methods have been raised, **(29-30)** and it is unlikely that this abnormality will explain more than a small minority of SIDS cases. Despite a call to the contrary, **(31-32)** there seems to be little justification for a widespread program of electrocardiographic screening to identify potential SIDS victims. Fatal arrhythmias from occult long QT syndrome may be responsible for some cases of sudden infant death syndrome (SIDS). Because patients who have long QT syndrome with sodium channel gene (*SCN5A*) defects have an increased frequency of cardiac events during sleep, and a recent case is reported of a sporadic *SCN5A mutation* in an infant with near SIDS, *SCN5A* has emerged as the leading candidate ion channel gene for SIDS. Approximately 2% of this prospective, population-based cohort of SIDS cases had an identifiable *SCN5A* channel defect, suggesting that mutations in cardiac ion channels may provide a lethal arrhythmogenic substrate in some infants at risk for SIDS **(33).**

This entity could belong to BrD, as demonstrated by genetic tests(34). It is more frequent in male new born babies , with a prevalence of 0,1% to 0,3% of all born alive.

There are a report that results support a proposed linkage between BrD and some instances of sudden infant death and the hypothesis that reduced Na(+) conductance is the primary cause of idiopathic ventricular fibrillation with S-T segment elevation **(35**). A missense mutation of SCN5A that substitutes glutamine for leucine at codon 567 (L567Q, in the cytoplasmic linker between domains I and II) is identified with sudden infant death and Brugada syndrome in one family. However, neither the functional effect of the L567Q mutation nor the molecular mechanism underlying the pathogenicity of the mutation is known. Patch-clamp analysis of L567Q channels expressed in human embryonic kidney cells revealed a marked acceleration and a negative shift in the voltage dependence of inactivation. Unlike other Brugada mutations, this phenotype was expressed independently of temperature or auxiliary beta (1)-subunits.

There is no consensus between different authors whether it is an apnea because of immature respiratory center dysfunction or obstructive apnea as causes of SIDS.
The American Academy of Pediatrics has recommended since 1992 that infants be placed to sleep on their backs to reduce the risk of sudden infant death syndrome (SIDS). Since that time, the frequency of prone sleeping has decreased from >70% to ~20% of US infants, and the SIDS rate has decreased by >40%. However, SIDS remains the highest cause of infant death beyond the neonatal period, and there are still several potentially modifiable risk factors. Although some of these factors have been known for many years (eg. maternal smoking), the importance of other hazards, such as soft bedding and covered airways, has been demonstrated only recently. The present statement is intended to review the evidence about prone sleeping and other risk factors and to make recommendations about strategies that may be effective for further reducing the risk of SIDS. This statement is intended to consolidate and supplant previous statements made by this Task Force **(36).**

The numbers **2, 3, 4, 5, 6** and **7** are allelic diseases, because are genes that occupy the same position or locus.

9) Liddle's syndrome:
Sodium channelopathy that affect the subunit subunit β or γ by mutation in amino acid carboxyl residues 47 and 75. Transmitted by autosomic dominant tract. Clinically it produces early high blood pressure with hypokalemia and suppression of plasmatic renin activity **(37-38).**

10) High blood pressure of negro race.

B) Neurological diseases:

1) Sodium channelopathies:

a) Familial generalized epilepsy with febrile seizures. Generalized epilepsy with febrile convulsions plus is caused by an abnormal sodium channel;
b) Hyper- and hypokalemic periodic paralysis;
c) Congenital paramyotonias;
d) Hypokartemic periodic paralysis
e) Myotonias

2) Potassium channelopathies:

a) Benign infantile epilepsy**.** Benign neonatal familial convulsions are secondary to a mutated potassium channel; **(39).**
b) Episodic ataxia type 1.

3) Calcium channelopathies:

a) Episodic ataxia type 2;
b) Spinocerebellar ataxia type 6 (SCA6) belongs to the group of autosomal dominant cerebellar ataxias (ADCAs) as well as to the group of channelopaties. The expandible sequence is embedded in a calcium channel gene, CACNA1A, on chromosome 19p13, coding for the _1A subunit of voltage-gated calcium channels type P/Q, of which several isoforms are known not all expressing the CAGn sequence. SCA6 differs in many respect from ADCAs caused by CAG expansions, and is unique, among channelopathies , for not being due to point mutations. Point mutation at the CACNA1A gene are known to cause Episodic Ataxia type 2 (EA2) and Familial Hemiplegic Migraine (FHM). These disorders, and particularly EA2, share many features with SCA6, posing the problem of the relationship among the 3 allelic diseases and of the phenotype-genotype correlation.
This presentation will review and discuss the, often confusing, literature data on clinical, pathological, biophysical and genetic aspects of SCA6 as compared to its two allelic disorders, and other SCAs, with the aim of a) delineating more clearly the SCA6 phenotype and the extent of its overlap with EA2 and FHM ; b) indicating possible pitfalls in the clinical assessment of SCA6 patients ; c) defining the range of variation for the normal and the expanded SCA6 alleles ; d) focusing on the problem of CAGn expressing and non-expressing _1A subunit isoforms ; e) highlighting analogies and differences among SCA6 mutation, CACNA1A point mutations, and other disease-causing CAGn expansions, with particular reference to their providing a gain or a loss of function to the protein; f) delineating fields in which collaborative research on SCA6 will be particularly productive;
c) Familial hemiplegic migraine;
d) Hypokalemic periodic paralysis;
e) Central core disease;
f) Malignant hyperthermia syndrome;
g) Other mechanisms that may be responsible for epileptogenesis include altered inhibitory and excitatory neurotransmission and abnormal calcium currents.
h) Hypocuartemica periodic paralysis;
i) Myasthenic Lambert-Eaton Syndrome.

4) Chloride channelopathies:

a) myotonia congenitas.

5) ACh receptor channelopathies: ligand-gated (nicotinic acetylcholine receptor subunits)

a) autosomal dominant frontal lobe nocturnal epilepsy; is due to a mutation of the alpha 4 subunit of the nicotinic receptor **(40).**

b) congenital myasthenic syndromes;

6) Glycine receptor channelopathies:

a) Hyperekplexia.

C) Psychiatric diseases

1) Schizophrenia

2) Alzheimer's disease: Alzheimer disease is the most common and well-known form of dementia. It rarely occurs before the age of 60, and affects approximately 6% of individuals older than 65 years of age. The disease afflicts one third of the population aged 85 and over. Alzheimer is more common in women than in men. Given the continual ageing of the population, the number of cases is on the rise.
Alzheimer's disease causes 50% to 70% of all dementia. Although researchers are finding that some of what was previously considered Alzheimer's are really one of two other degenerative diseases: diffuse cortical Lewy body disease and Pick's disease. The second most common cause of dementia after Alzheimer's is vascular dementia. About 20% to 30% of all dementia is believed to be caused by some sort of vascular dysfunction, the most common of which is multi-infarct disease.
Research into Alzheimer disease has not yet identified the definitive cause of this pathology. Nonetheless, scientists have identified that the cells responsible for the production of acetylcholine (a neurotransmitter or messenger between brain cells) die in great numbers at hipocampus as the disease progresses. Without acetylcholine, communication between the cells becomes impossible, explaining the progressive loss of cognitive functions. In certain cases, it seems that defective hereditary genes may be responsible for this progressive and premature destruction.

D) Ophthalmologic diseases

1) Congenital stationary night blindness: it is a calcium channelopatie.

2) Total colour-blindness

E) Other diseases

1) Bartter's syndrome: renal tubulopathy autosomic recessive that affected primarily absorption of anion chloro channel in ascendant Henle loop of kidney with loss of chloro, sodium, potassium, whether and secondary hyperaldosteronism without hypertension. The Bartter´ s syndrome affected (to) the potassium channels. There are hyperkaliuria and hypokalemia and secondary metabolic alkalosis;

2) Polycystic kidney disease: It is an autosomal dominant disease that affect the short arm of chromosome 16.

3) Dent's disease

4) Hyperinsulinemic hypoglycemia of infancy

5) **Cystic fibrosis or mucoviscidosis:** autosomal recessive disease, modifies chromosome 7 affecting an intrinsic protein called CFTR (cystic fibrosis trasmembrane conductance regulator) **(41).** that controls the chloride anion. In 70% of the cases there is deletion of phenylalanine of the protein position 508. Another 500 different types have already been identified. White population is more frequently affected **(42) .** 1/2000 children. It is due to the ionic abnormal composition of the exocrine gland and secretion of mucus with a viscous physico-chemical composition obstructing the ducts conducting to DPOC, insufficiency in the pancreatic enzyme secretion, enteric obstruction, cirrhosis, and other disturbances **(43).** In 90% of the cases it is complicated with repetitive lung infection by pseudomona aeruginosa, this being the most common cause of obitus in these ill people. In Brazil, about 50% of the patients die before completing 10 years of age. The average incidence in the country would be of 1 case among 7.358 born, in Rio Grande do Sul 1 among 1.587. Nowadays, the Government authorized the test of the little foot to detect cystic fibrosis, falciform disease and hemoglobinopathies. Only one drop of blood can be enough to make diagnosis using the Raskin test.

In recent revision, the Professor of Medicine, Physiology and Biomedical Engineering Eduardo Marban, from the Division of Cardiology of John Hopkins School of Medicine teach us that the concept of channelopathies is not restricted to genetic disorders; notably changes in the expression or pos-translational modification of ion channels underlie the fatal arrhythmias associated with heart failure. Recognizing the fundamental defects in channelopathies provides the basis for new strategies of treatment, including tailored pharmacotherapy and genetic therapy **(44).**

The Drugs, can induced channelopaties. An example is cocaine that by two distinct clinical profiles emerge from case reports of electrocardiographically documented life-threatening arrhythmias attributed to the drug. The first one is idioventricular rhythm that occurs in overdose situations and appears to reflect excessive sodium channel block; it may respond to sodium bicarbonate. The second is torsade de pointes that occurs in recreational users who have underlying risks for this ventricular tachycardia (such as fully or partially expressed congenital long QT syndrome) and reflects potassium channel blockade. These clinical observations can be explained by recent findings regarding the electrophysiologic effects of cocaine. Other patterns of severe arrhythmias due to cocaine may yet emerge **(45).**

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