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REVIEW ARTICLE

Mechanisms of inherited cardiac conduction disease

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Abstract Cardiac conduction disease (CCD) is a serious disorder of the heart. The pathophysiological mechanisms underlying CCD are diverse. In the last decade the genes responsible for several inherited cardiac diseases associated with CCD have been identified. If CCD is of an inherited nature (ICCD), its underlying mechanism can be either structural, functional or there can be overlap between these two mechanisms. If ICCD is structural in nature, it is often secondary to anatomical or histological abnormalities of the heart. Functional ICCD is frequently found as a ''primary electrical disease'' of the heart, i.e. resulting from functionally abnormal, or absent proteins encoded by mutated genes, often cardiac ion channel proteins involved in impulse formation.

It can thus be hypothesised that patients with inherited structural or functional ICCD suffer from fundamentally different diseases. It is worthwhile to consider this hypothesis, since it could have implications for diagnosis, treatment, prognosis and, possibly, for the patient's relatives.

In this review we aim to find evidence for the idea that functional and structural ICCD are fundamentally different diseases and, if so, whether this has diagnostic and clinical consequences.

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Introduction

Cardiac conduction disease (CCD) is a serious, and a potentially life threatening disorder of the heart [1]. In CCD, the integrity of the conduction system is impaired, such that impulse conduction will be slowed or even blocked and life-threatening rhythm disturbances may ensue. The pathophysiological mechanisms underlying CCD are diverse, but irrespective of its cause, the ultimate treatment may be pacemaker implantation [1,2]. Notwithstanding that, it is worthwhile to consider the pathophysiological basis of CCD in more detail, since it may have implications for diagnosis, development of new treatment strategies, and prognosis. Also, if an inherited form of CCD is suspected, this knowledge may have consequences for family members of the affected individual.

Historically, CCD was viewed purely as a structural disease of the heart in which macro- or microscopical structural abnormalities in the conduction system underlie disruption of normal impulse propagation. In a substantial number of cases, however, conduction disturbances are found to occur in the absence of anatomical abnormalities. In these cases, functional rather than structural alterations appear to underlie conduction disturbances (Fig. 1). Frequently functional CCD is found to be a so-called 'primary electrical disease' of the heart, a group of inherited diseases that result from functionally abnormal, or absent, proteins encoded by mutated genes [3—5]. The affected proteins are often cardiac ion channel proteins involved in cardiac impulse formation.

It can thus be hypothesised that patients with inherited structural or functional CCD suffer from fundamentally different diseases, although overlap between the two pathophysiological mechanisms may still exist.

In this review we aim to categorise and discuss reports on congenital and inherited CCD to find supportive evidence for these ideas. The questions we have attempted to answer while reviewing these reports were: 1) is the reported disease congenital and if so, inherited or acquired? 2) what is known about the pathophysiological mechanism of the reported disease? 3) can we relate reported clinical parameters to a particular pathophysiological mechanism? and finally, 4) are structural and functional CCD indeed different diseases?

The cardiac conduction system

Structural components

Before we continue our consideration of the fundamental differences between structural and functional CCD, we should appraise the structures involved in conduction in the heart. The cardiac conduction system enables fast and co-ordinated contraction of the heart. It is composed of

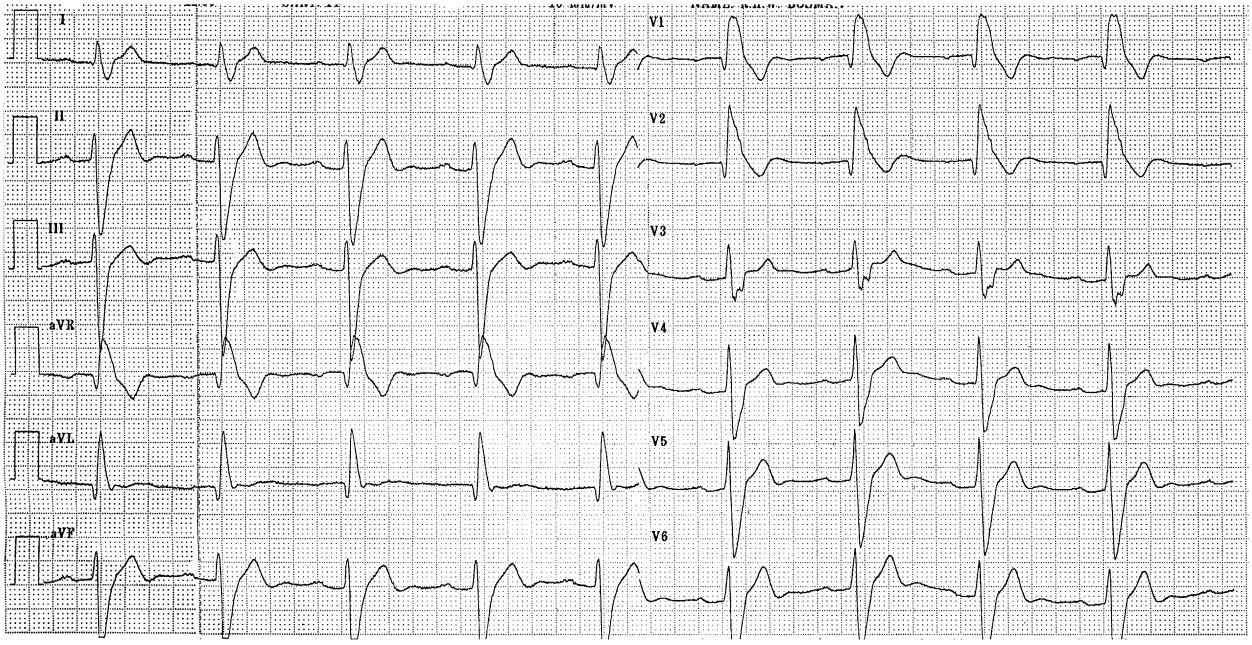

Figure 1 12-lead ECG of a patient with ICCD due to an *SCN5A* mutation. Note the widened PQ and QRS-intervals (paper speed 25 mm/sec, calibration 10 mm/mV).

specialized cardiac structures that are responsible for impulse formation and propagation. The cardiac impulse is generated by the sinus node in the right atrium, and is conducted to the left atrium via the Bachmann bundle. From the atria, electrical activity is transmitted to the ventricular myocardium through the atrioventricular node, the bundle of His, the right and left bundle branches, and the Purkinje fibre network successively, to ensure synchronized contraction of the heart.

Macro- or microscopical structural abnormalities in CCD may occur at any level in the conduction system and disrupt normal impulse propagation. These structural abnormalities may range from partial or total absence of structures, to gradual replacement of the normal tissues by fatty and/or fibrous tissue and calcification.

Functional components

The cardiac impulse, or action potential, is generated in the sinoatrial node through the combined action of several different types of ion conducting proteins [3—6]. Briefly, the main players in the upstroke and repolarization of the SA node action potential are the depolarizing L- and T-type calcium currents and the repolarizing delayed rectifier potassium currents respectively [6]. The repolarization of the action potential is followed by the diastolic depolarization, a slow spontaneous depolarization towards the threshold for generating another action potential. For fast propagation of the action potential through the atria, His-Purkinje system and the ventricles, the voltage gated sodium channel and gap junctions are of major importance [3—5]. The speed of depolarization of the cells in these tissues, which is represented by the upstroke velocity of the action potential, is dependent on the magnitude of the sodium current and thus on sodium channel function and availability [4]. The depolarizing current is transmitted from cell to cell through intercellular channels, the gap junction channels [7,8]. These channels are constructed of two hemichannels, each composed of 6 protein subunits, the connexins [9].

Developments in molecular biology and genetics have increased our understanding of the molecular mechanisms of inherited cardiac conduction abnormalities and arrhythmia syndromes in general. We now know that these familial primary electrical diseases of the heart, that occur in the absence of structural heart disease or systemic disease, result from mutations in cardiac ion channel genes and associated or modifying proteins, such as cytoskeletal proteins [3,10].

Methods

The Medline/OVID literature database was searched for original reports using the search terms: cardiac, conduction, congenital, genetics, heart, inherited, Lenegre, Lev, *SCN5A* and sodium channel. In addition, relevant references in this set of papers which were not identified by the Medline/Ovid literature database, were also retrieved. To complete our database we checked for follow up reports on the original publications. We have limited our search to original reports on cardiac phenotypes.

Reviewing and comparing data from original reports (Tables 1—3) that span more than 50 years of scientific progress, comes with some problems. Firstly, the earlier reports are mainly case reports of small groups of patients, or individual patients. For the study of the inherited nature of diseases and genetic screening, large patient-groups are needed. Such screening could not be performed in earlier times, since the techniques for genetic analysis have become available only very recently. Only in the more recent studies, the presence of mutations in the *SCN5A*, *PRKAG2*, *NKX2-5* and *LMNA* genes was investigated. These genes were recently found to be linked to cardiomyopathies (isolated), conduction disease and (isolated) arrhythmias (Tables 1—3). Secondly, in most reports the presence of discrete structural, histological abnormalities of the heart and the specialized conduction system cannot always be excluded because of the limited diagnostic possibilities in those days or because they were not sought for. Also, some individuals reported to have CCD may have been suffering from other cardiac diseases associated with fainting spells and arrhythmias that have only recently been recognized, such as the Brugada syndrome.

History

Historical description of cardiac conduction disease

Without actual electrical recordings we are left guessing at the mechanisms of what are the first descriptions of ''fainting spells''. It was not until the beginning of the 20th century that the development of the electrocardiogram by Willem Einthoven (1860—1927) made electrical recordings

of impulse conduction through the heart possible. Giovanni Battista Morgagni (1682–1771) [11], however, was probably the first to link recurring fainting episodes in a man to a simultaneously observed slow pulse rate. In the 19th century first Robert Adams (1827) [12] and later William Stokes (1854) [13] made similar observations. The first known report of an Adams-Stokes attack combined with ECG recordings came from van den Heuvel [14] who described a case of congenital heart block. Lenegre and Lev combined clinical observations, ECG recordings and detailed post mortem studies of the heart, whereby they proved their direct relationship in the 1960's [15–18] The names Lenegre and Lev have thenceforth become synonymous with (progressive) cardiac conduction disease. Electrocardiographically, both Lenegre and Lev disease are characterized by chronic conduction delay through the His-Purkinje system, resulting in partial or complete AV-block and right or left bundle branch block [15–18]. In both diseases a sclerodegenerative process causes fibrosis of the His-Purkinje fibres. The severity and extent of the fibrosis in these diseases, however, is different [15–18]. In Lenegre disease, a diffuse fibrotic degeneration is limited to the conduction fibres, while in Lev disease the sclerodegenerative abnormalities affect both the specialized conduction system and the fibrous skeleton of the heart. An inherited component may be involved in both diseases. However, particularly Lev disease may be a variation of the normal ageing process [19].

Congenital or inherited abnormalities in cardiac conduction

The recognition that CCD can as well be inherited as acquired, dates from the beginning of last century. In 1901 Morquio described, what was probably congenital complete atrioventricular block in a family [20]. The disease was presented with syncopal periods and slow pulse rates. Congenital heart block had, at that time, already been reported in newborns from mothers suffering from connective tissue diseases. Other, early recognized causes for congenital CCD are infectious diseases such as diphtheria, rheumatic fever and congenital syphilis [21–23]. Due to the absence of electrocardiographic, or histological analysis, exact diagnosis is difficult in these early cases of congenital CCD.

The discovery of gene mutations that are causally involved in inherited CCD is relatively recent. Nowadays for example, mutations have been found in genes encoding (transcription) factors that regulate cardiac morphogenesis. Such mutations cause inherited CCD due to, or in combination with, cardiac malformations [24–31].

Similarly, mutations have been found in inherited non-structural CCD, often encoding cardiac ion channel proteins [32–44]. Some genes involved in non structural inherited CCD, however, remain to be identified. A good example are two reports from 1977 on two types of progressive congenital or familial heart block (PFHB), type I and II, among families in South Africa [45,46]. In 1995, PFHB type I was linked to a gene located on chromosome 19q13.2–q13.3 [47,48]. This discovery proved the inherited nature of the disease but the pathophysiological mechanism, the affected protein and the genetic defect have not yet been identified.

Structural CCD

In the case of structural CCD, anatomical abnormalities underlie the impairment of normal impulse propagation. This concerns macro- or microscopical structural abnormalities that may occur at any level in the conduction system. The structural abnormalities, as mentioned, may range from partial or total absence of structures to gradual replacement by fatty and/or fibrous infiltration and calcification. In many reports, the term structural heart disease is reserved for overt anatomical abnormalities of the heart and does often not include the specialized conduction system, which is often not studied (Tables 1–3). Therefore, hearts that are considered to be structurally normal may still have histological abnormalities, such as focal myocarditis or segmental cardiomyopathy. Structural CCD may be either congenital or inherited (Fig. 2).

Structural CCD of congenital nature

The causes of congenital structural CCD are many, they can be part of a syndrome and be associated with abnormalities in other organ systems. For example, anatomical heart defects may occur in chromosomal disorders like Down's, Edward's, Pateau's or Turner's syndromes [22,23]. Although congenital anatomical heart defects frequently occur in these and other chromosomal disorders, still in the majority of cases no chromosomal abnormalities can be found [22,23]. Other causes of structural heart disease may be intra-uterine exposure to infectious or toxic agents (e.g. nicotine, drugs) [22,23]. As mentioned before,

Table 1 Patients with inherited cardiac conduction disease related to anatomical abnormalities of the heart and/or the specialized conduction system

Reference	Number of cases/ investigated	Sex	Age of onset (yr)	ECG characteristics	Abnormal anatomy heart	Abnormal anatomy conduction system	Histology myocardium	Histology conduction system	Inheritance	Proposed mechanism
Wendkos 1947 [84]	6/3	?	B	Complete AV block WPW	Y	Y	–	–	AD	Structural? possibly no His bundle
Griffith 1965 [85]	8/5	?	C	1,2nd/complete AV block/SCD	–	NA	H+F	NA	AD (?)	Cardiomyopathy (?)
Lev 1967 [83]	2 cases	?/♀	IU/C	Complete AV block	ASD	Y/Y	I+F	I+F	?	Secondary to ASD/absent AV node
Lev 1971 [18]	1 case	–	C	CHB/VT/VF/ complete AV block	Hypertrophy postductal coarctation	Y	FE+C	FE+C	?	Disruption penetrating portion of the AV bundle/F+FE+C
Lev 1971 [18]	1 case	–	B	Complete AV block	ASD	Y	FE+C	FE+C	?	Disruption penetrating portion of the AV bundle/F+FE+C
Waxman 1975 [86]	28/6	♂>♀	A (>40y)	pr. AV block ''abnormal QRS'' AF/VT/SCD	+	SA node: F AV node:F His bundle:F	–	NA	AD	Progressive fibrosis
Anderson 1977 [87]	1 case	♀	B	CCHB	+	Abnormal connection A and AV node/ no RBB	NA	NA	Case	Abnormal anatomical development
Anderson 1977 [87]	1 case	♂	IU	Bradycardia IU/ CCHB/small QRS/frequent PVC's	ASD/F	Abnormal connection A and AV node/ no RBB	NA	NA	C	Abnormal anatomical development
Anderson 1977 [87]	1 case	♀	IU	Bradycardia IU/ CCHB/small QRS	Hypoplastic central fibrous body	Discontinuity AV junction and Ventricle	NA	NA	C	Abnormal anatomical development
Stephan 1985 [88]	19/5	♂>♀	A	RBBB+LAD/CHB/ progressive	None	None	F central fibrous body and part of ventricular septum	Fibrosis His bundle, LPF, LAF, RBB	AD	Lev disease, progressive
Bezzina 2003 [37]	5/2	♂=♀	B	Broad complex tachycardia/atrial and ventricular conduction delay/SCD	VH+D	Y	FE+C+N+I	F	CH	W156X/R225W *SCN5A* mutations/sec. to prog. degenerative process
Miller 1972 [89]	1 case	♀	IU/B	Complete AV block RBBB+ LAHB RBBB+LPHB	Y	Y	FE	F+C	?	Absent AV node/no communication atria-AV node
Schott 1998 [25]	4 families (n=29, 15, 11 and 9)	♂/♀	?	Progressive AV block/ 16% AV block no structural heart defects/SD	Cardiac septation defects	NA	NA	NA	AD	Mutation in homeobox transcription factor gene *NKX2-5* (T178M, Q170ter)
Benson 1999 [29]	4 families (n=11, 15, 13 and 7) +2 groups*[1]	♂/♀	?	1–3rd degree AV block, AV block principal finding in 23% of cases	Cardiac septation defects	NA	NA	NA	AD	Mutation in homeobox transcription factor gene *NKX2-5* (Q149ter, R186G, Y259ter and N188K)
Hosoda 1999 [31]	1 family (n=8)	?	AA	AV block/AF with slow AV conduction	ASD	NA	NA	NA	AD?	Mutation in homeobox transcription factor gene *NKX2-5* (Q198ter)

Gutierrez-Roelens 2002 [27]	2 families (n=28 and 18)*2	♂/♀	?/A	Progressive AV block	Cardiac septation defects	?	?	?	AD	mutation in homeobox transcription factor gene *NKX2-5* (R142C and Q187H)
Wanatabe*3 2002 [30]	2 families (n=15 and 9)	♂/♀	?/A	1–3rd degree AV block/AF	Cardiac septation defects	?	?	?	AD	mutation in homeobox transcription factor gene*NKX2-5*(deletion)
Gollob 2001 [69]	1 family (n=10)	?	AA	AF and atrial flutter, high progressive high grade conduction disease	N	Assessory bundle	?	?	AD	mutation in *PRKAG2* gene encoding a protein kinase regulatory subunit (R531G)
Gollob 2001 [70]	2 families (n=69 and 23)	?	A	Bradyarrhythmia/SA, AV block progressive/ affected individuals >30yrs 76% need pacing	N	Assessory bundle, hypertrophy (n=3)	?	?	AD	mutation in *PRKAG2* gene encoding a protein kinase regulatory subunit (R302Q)
Fatkin *3 1999 [63]	5 families (n=11, 12,7, 10 and 11)	♂=♀	A	SB, 1–3rd degree AV block/AF, PM	DCM	?	F/H	1 case F, fatty infiltration SA, AV node and AV bundle	AD	mutation in *LMNA* gene encoding lamin A/C (R60G, L85R, N195K, E203G and R571S)
Jakobs 2001 [64]	2 families (n=64 and 66)	♂=♀	A	1–3rd degree AV block, LBBB, AF, AFl, VES, AES, PM, SD	DCM	?	?	?	AD	Mutation in *LMNA* gene encoding lamin A/C (E203K and R225X)
Herschberger*3 2002 [65]	1 family (n=12)	♂=♀	A	1–3rd degree AV block, LBBB, PM, AF, AFl, AES, VES, SD	DCM	?	?	?	AD	Mutation in *LMNA* gene encoding lamin A/C (L215P)
Arbustini*3 2002 [66]	5 families (n=25)	♂=♀	C/A	SB, 1–3rd degree AV block, PM	DCM	?	DCM	?	AD	Mutation in *LMNA* gene encoding lamin A/C (K97E, E111X, R190W and 317K)
Sebillon*3 2003 [67]	1 family (n=5)	♂=♀	A	1–3rd degree AV block, AF, PM, SD	DCM	?	DCM	?	AD (?)	Mutation in *LMNA* gene encoding lamin A/C (E161K and R377H)
Charnoit *3 2003 [68]	1 family (n=12)	♂=♀	A	1–3rd degree AV block, LBBB, (i) RBBB, PM, AF, SD	DCM	?	DCM/F/H	?	AD	Mutation in *LMNA* gene encoding lamin A/C (R377H)
Taylor*3 2003 [60]	2 families (n=5)	♂=♀	A	1st degree AV block, AF, AES, VES, VT, SD	DCM	?	?	?	AD	Mutation in *LMNA* gene encoding lamin A/C (G266T and C1718T)

ABBREVIATIONS: Column age of onset: AA=all ages, A=adulthood, B=birth, C=congenital, IU=in utero. Column ECG characteristics: AF=atrial fibrillation, AFl=atrial flutter, AV=atrioventricular, CCHB=congenital complete heart block, CHB=complete heart block, IVF=idiopathic ventricular fibrillation, LAD=left axis deviation, LAF=left anterior fascicle, LAHB=left anterior hemiblock, LPF=left posterior fascicle, LPHB=left posterior hemiblock, PB=parietal block, PM=artificial pacemaker, PVC=premature ventricular complex, RBBB=right bundle branch block, SB=sinus bradycardia, SD=sudden death, TdP=Torsade des Pointes, VT=ventricular tachycardia, VF=ventricular fibrillation, WPW=Wolff-Parkinson-White syndrome. Columns abnormal anatomy and histology heart, conduction system: A=atrium, ASD=atrial septal defect, C=calcification, CTD=connective tissue disease, DCM=dilated cardiomyopathy F=fibrosis, FE=fibroelastosis, H=hypertrophy, I=inflammation, V=ventricle. Column inheritance: AD=autosomal dominant, C=case, CH=compound heterozygosity. *1 additional 1 patient group with idiopathic 2nd or 3rd degree AV block was studied for NKX2-5 mutations and a second group with Tetralogy of Fallot. *2 additional 16 individuals with a familial history of cardiomyopathies and 34 isolated cases were studied. *3 cases of CD (AV) occur without structural disease.

Table 2 Patients with inherited cardiac conduction disease related to an *SCN5A* mutation

Reference	Number of cases/ investigated	Sex	Age of onset (yr)	ECG characteristics	Abnormal anatomy heart	Abnormal anatomy conduction system	Histolgy myocardium	Histology conduction system	Inheritance	Proposed mechanism
Probst 2003 [36]	65/25	♂=♀		RBBB/LPHB/iRBBB/LBBB/ LAHB/LPHB/PB/1st degree AV block/CHB	None	NA	NA	NA	AD	*SCN5A* mutation/exon 22-deletion/non-fuctional sodium channel
Tan 2001 [33]	10/5	♂<♀	C	Bradycardia, AV-nodal escape, broad P, long PR, wide QRS	None	NA	NA	NA	AD	*SCN5A* mutation G514C/febrile illness induced
Shirai 2001 [34]	25 IVF cases/ 1 patient	?	?	1st degree AV-block Rate dependent RBBB/IVF	NA	NA	NA	NA	?	*SCN5A* mutation S1710L
Schott 1999 [32]	Family 1>150/15 family 2 6/3	?	1. AA 2. B	RBBB, LBBB, left ant/posterior hemiblock, PR>210	None	NA	NA	NA	AD	*SCN5A* missence mutation/ progressive
Schott 1999 [32], Herfst 2003 [42]	9/5	♂=♀	B	Broad p-wave/ 1st degree AV block/BBB	None	NA	NA	NA	AD	Missence *SCN5A* mutation 5280delG/trafficking defect no channels on the cell membrane
Valdivia 2002 [43]	1 case	♂	B	2:1 AV block QTc prolonged/TdP/SCD	NA	NA	NA	NA	de novo mutation	M1766L *SCN5A* mutation reduced channel expression persistent INa
Bezzina 2003 [37]	5/2	♂=♀	B	Broad complex tachycardia/atrial and ventricular conduction delay/SCD	VH+D	Y	FE+C+ N+I	F	CH	W156X/R225W *SCN5A* mutations/sec. to prog. degenerative process
Wang 2002 [35]	6/3	Both	C	1st degree to complete AV block/RBBB	NA	NA	NA	NA	?	*SCN5A* mutation D1595N/I_{Na} reduced
Wang 2002 [35]	1 case	?	C	2nd 3rd degree A-V block	NA	NA	NA	NA	AD/?	*SCN5A* mutation G298S/I_{Na} reduced
Viswanathan 2003 [44]	5/2	♂=♀	C	2th degree AV-block	NA	NA	NA	NA	AD/?	*SCN5A* mutation T512I/I_{Na} ↓ modification by SCN5A polymorphism H558R
Groenewegen 2003 [38]	44/10	?	A	AS/AV-block	None	NA	NA	NA	AD	*SCN5A* mutation, D1275N isolated or combined with a connexin 40 polymorphism

ABBREVIATIONS: Column age of onset: AA=all ages, A=adulthood, B=birth, C=congenital, IU=in utero. Column ECG characteristics: AF=atrial fibrillation, AFl=atrial flutter, AV=atrioventricular, CCHB=congenital complete heart block, CHB=complete heart block, IVF=idiopathic ventricular fibrillation, LAD=left axis deviation, LAF=left anterior fascicle, LAHB=left anterior hemiblock, LPF=left posterior fascicle, LPHB=left posterior hemiblock, PB=parietal block, PM=artificial pacemaker, PVC=premature ventricular complex, RBBB=right bundle branch block, SB=sinus bradycardia, SD=sudden death, TdP=Torsade des Pointes, VT=ventricular tachycardia, VF=ventricular fibrillation, WPW=Wolff-Parkinson-White syndrome. Columns abnormal anatomy and histology heart, conduction system: A=atrium, ASD=atrial septal defect, C=calcification, CTD=connective tissue disease, DCM=dilated cardiomyopathy F=fibrosis, FE=fibroelastosis, H=hypertrophy, I=inflammation, V=ventricle. Column inheritance: AD=autosomal dominant, C=case, CH=compound heterozygosity. *[1] additional 1 patient group with idiopathic 2nd or 3rd degree AV block was studied for NKX2-5 mutations and a second group with Tetralogy of Fallot. *[2] additional 16 individuals with a familial history of cardiomyopathies and 34 isolated cases were studied. *[3] cases of CD (AV) occur without structural disease.

Table 3 Patients with inherited cardiac conduction disease of unknown origin

Reference	Number of cases/ investigated	Sex	Age of onset (yr)	ECG characteristics	Abnormal anatomy heart	Abnormal anatomy conduction system	Histology myocardium	Histology conduction system	Inheritance	Proposed mechanism
Brink 1977, 1995 [45,47] van der Merwe 1986 [46]	1 family 55/ 31 investigated	♂=♀	IU	RBBB/LAHB/broad QRS/CHB/SCD	NA	NA	NA	NA	AD	Disease linked to chromosome 19q13.2–13.3/progressive
Brink 1977 [45]	1 family 24/10 investigated	♂=♀	?	SB/LPHB/narrow QRS/CHB/SCD	NA	NA	NA	NA	AD	Degeneration of the conduction paths
Lynch 1975 [91]	1 family 255/40	♂=♀	C	1st degree-complete AV block/SB/atrial or ventricular arrhythmia/SCD	None	None	None	None	AD	?/progressive
Lynch 1973 [90]	166/26	?	A							
Sarachek 1972 [101]	43/15	♂=♀	C	SB/CHB/1st & 2nd degree AV block/RBBB+LAHB/SCD due to CHB and eci.	None	NA	NA	NA	?	?
Stephan 1978 [102], Meeuws 1995 [47]	209/32	♂>♀	IU/B	(ic)RBBB/LAD/RAD CHB/ still birth CCHB/SCD	NA	NA	NA	NA	AD	Disease linked to locus 19q13.3/ mechanism ?
Stephan 1979 [102]	1 kindred 3 families	♂>♀	AA	CHB/(ic)RBBB/LAHB/ RBBB+LAHB	None	NA	NA	NA	AD	?/progressive
Gazes 1965 [96]	35/11 (8 documented with ECG)	♂=♀	IU/B	SB AV-block 1 and 2 degree/complete block RBBB/SCD	—	—	Hypertrophy and dilatation 1 case	—	AD	Unknown
Simonsen 1970 [98]	30/5	♀>♂	C	SR, bradycardia 1-2-3rd degree AV-block LBBB/RBBB	NA	NA	NA	NA	AD	?/variable clinical picture/ progressive ?
James 1975 [104]	2 siblings	♂=♀	B	CCHD	1 case Y	1 case Y	I	I/N	?	?
Combrink 1962 [98]	10/6	♂=♀	B	AV-dissociation CHB/RBBB/SCD	—	—	—	—	AD	''structural fault in the conducting bundle….or a enzyme derangement in fibres of the RBB''
McCue 1977 [49]	22 (4)*[1]	♂=♀	C	CCHB	NA	NA	NA	NA	?	14x maternal CTD associated, 4x ?, non structural
Winkler 1977 [50]	11/4	♂=♀	A/C	Bradycardia, AV block, CHB, RBBB, LBBB	+CTD associated cases	NA	I/C CTD associated cases	NA	?	Genetic (paternally transmitted)+maternal CTD (2 cases)
Veracochea 1967 [103]	8/3 (3† eci.)	?	B	Complete AV block	None	NA	NA	NA	?	?
Esscher 1975 [100]	91/20	?	B	RBBB	None	NA	NA	NA	AD	?/congenital
Balderston 1989 [95]	2 individuals in 1 family	♂	C	AV block/CHB/LBBB pattern	None	NA	NA	NA	AD	? non-structural, progressive

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infectious diseases like diphtheria, syphilis and rheumatic fever had a significant role in congenital CCD in the past. Although nowadays relatively less frequent, viral and bacterial infectious diseases still have a role in congenital CCD [21—23]. Finally, another important cause of congenital structural CCD, is intra-uterine exposure to maternal autoantibodies. Because the structural abnormalities in these cases may be very subtle or even absent, the underlying mechanism will be considered separately below.

Autoimmune mechanisms

Autoimmune diseases can affect the whole cardiovascular system including the cardiac conduction system [49—59]. CCD in autoimmune disease may be secondary to myocarditis because of inflammation and infiltration, as in Systemic Lupus Erythematosus (SLE), scleroderma and polymyositis [49—55]. Vasculitis and obliterative endarteritis are examples of autoimmune diseases that indirectly affect the myocardium by causing ischaemia [53—55]. Cardiac conduction may be affected to a variable degree in the various autoimmune diseases. In HLA-B27 associated diseases for instance, such as the seronegative spondylarthropathies, CCD is of frequent occurrence although structural abnormalities may be absent (see later) [56—59]. In this latter group the conduction abnormalities usually consist of A-V block, sinus node disease and bradycardia. These abnormalities can be permanent or intermittent. The latter argues for a reversible, functional, inflammatory process rather than fibrosis (see later) [54—59].

Structural CCD of inherited nature

Septation defects

Mutations have been identified in familial forms of cardiac malformations. These mutations have been found in genes encoding proteins that regulate septation of the heart, resulting in atrial septal defects (ASD) or ventricular septal defects (VSD) [24—31]. Mutations in *TBX5*, a T-box transcription factor, have been identified in patients suffering from Holt-Oram syndrome [24]. This

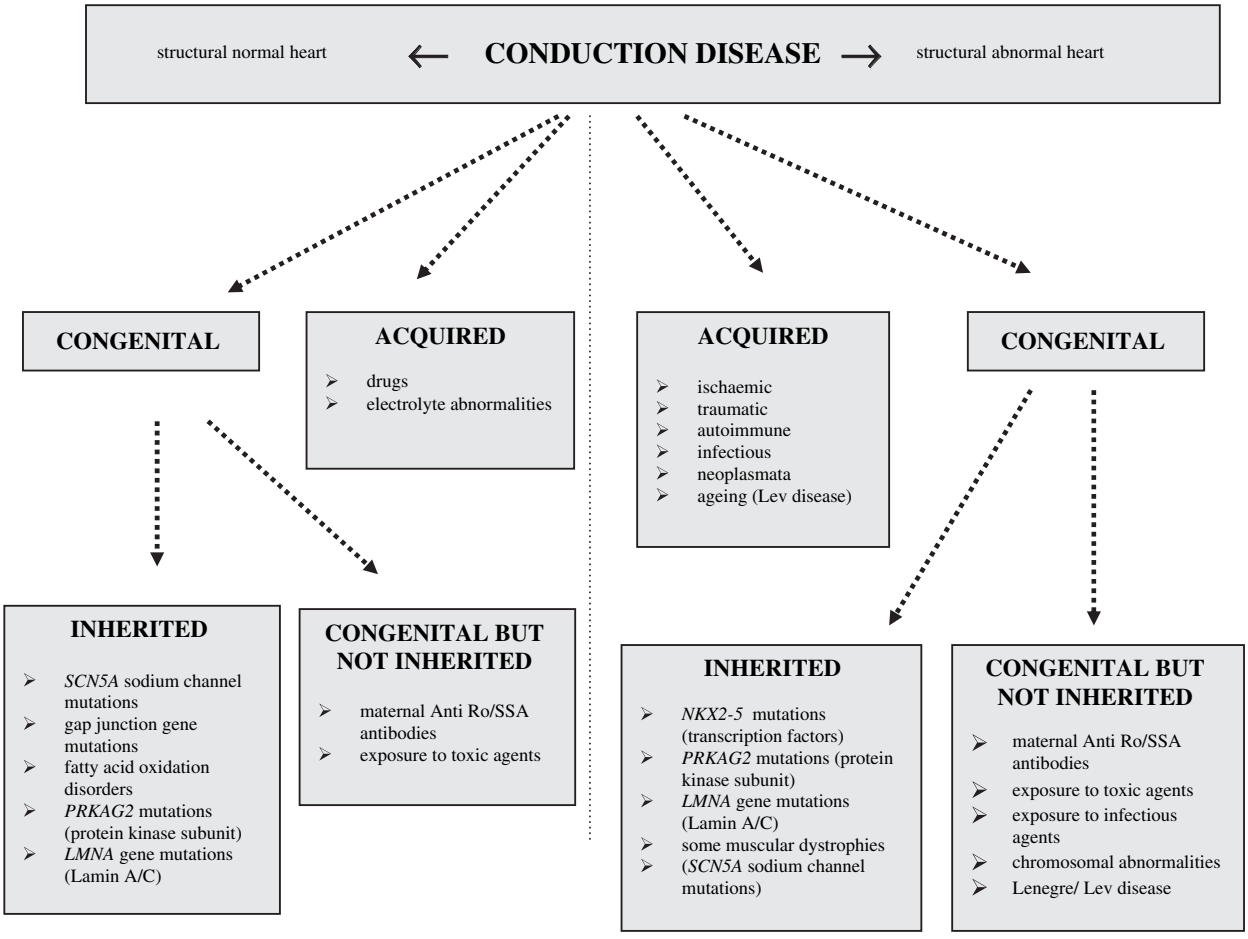

Figure 2 Flow diagram for conduction disease.

autosomal inherited syndrome is characterized by cardiac septation defects and extra-cardiac abnormalities. Sometimes, mutation carriers have CCD and atrial fibrillation in the absence of septation defects.

Mutations in *NKX2.5*, encoding a homeobox transcription factor, have been found in cases of familial ASD without extracardiac abnormalities (Table 1) [25—31]. Although the initial description was in individuals with autosomal inherited ASD and progressive AV block, it now seems that the clinical spectrum may be more diverse, including also VSD and tetralogy of Fallot. Finally, a number of familial cases of cardiac septation defects with progressive AV block have been diagnosed in which the involved proteins and genes still await identification.

The cytoskeleton

Mutations in genes encoding cytoskeletal proteins and nuclear membrane proteins have been found to be causally involved in inherited cardiomyopathies and muscular dystrophies (Table 1) [60—68]. An intact cytoskeleton is required for proper myocyte structure and is additionally involved in cell signalling processes.

Cardiac arrhythmias and conduction disease are common in patients suffering from muscular dystrophies and dilated cardiomyopathies (DCM) [60—62]. Mutations in the *LMNA* gene, encoding laminin, have been described to be causally involved in autosomal dominant Emery-Dreifuss muscular dystrophy, as well as in families with DCM and severe cardiac conduction defects without skeletal muscle involvement [60]. In these latter families, however, some individuals had severe conduction abnormalities in the absence of DCM or other clinically identified structural heart disease [60,63,65—68]. In these patients CCD probably precedes the development of DCM.

Protein kinase disorders

Recently a mutation (R302Q) in the PRKAG2 gene, which encodes for a regulatory subunit (γ-2) of adenosine monophosphate-activated protein kinase (AMPK), has been described (Table 1) [69]. This mutation was found in patients with the Wolff-Parkinson-White (WPW) syndrome, a disease characterized by ventricular preexcitation, atrial fibrillation and conduction defects. In 76% of the carriers of the R302Q mutation, in addition to preexitation, conduction disease was found, such as SA- and AV-block. Hypertrophy was found in 26 percent of the mutation carriers. Mutations in the *PRKAG2* gene thus cause structural heart disease, such as accessory conduction pathways between the atrial and ventricular myocardium, and cardiac hypertrophy [69].

Functional CCD

Functional CCD we defined as CCD without any structural, anatomical or histological abnormalities of the myocardium and its conduction system. In these circumstances the detrimental effects on cardiac conduction are usually due to altered function of cardiac ion channels or associated proteins, similar to the primary electrical diseases of the heart among which is inherited CCD. Like in structural CCD, we can distinguish acquired, congenital and inherited forms. Isolated CCD may precede other disease symptoms and in some cases functional CCD may be the first symptom of a disease that eventually will result in structural damage to the heart [63—68].

Acquired forms of functional CCD

Acquired functional CCD may be induced by several drugs, especially antiarrhythmic and anaesthetic drugs, and their effects are reversible. Additionally, there are several naturally occurring toxins, which may affect conduction. The working mechanism of these toxins on conduction is often through a direct effect on ion channel function. Disturbances of ion concentrations in intra- or extracellular fluids may additionally be a cause of CCD.

Functional CCD of congenital nature

Autoimmune mechanisms

Next to the inflammatory mechanism giving rise to structural forms of CCD in autoimmune diseases, there may also be a functional component in neonates born from mothers suffering from SLE or other connective tissue diseases [56—59]. Namely, in a number of cases, the congenital heart block may be transient and regress when the maternal IgG antibodies are washed out [56—59]. Usually these individuals have 1st degree A-V block combined with sinus bradycardia. Maternal SSA/Ro and/or SSB/La (IgG) antibodies that cross the transplacental membrane and enter the foetal circulation underlie this CCD [56—59]. In order to elucidate the mechanism, Boutjdir et al. retrogradely perfused a human foetal heart on a Langendorff perfusion system with purified IgG antibodies from a mother who gave birth to a child with CCD and who was diagnosed as having SLE. In this

system they were able to induce a partially reversible complete A-V block [57]. Similar results are obtained in different animal experimental models [56]. It is postulated that the block is due to modification of the L-type calcium channels in foetal A-V node myocytes by maternal IgG antibodies [59]. Although the number of cases where functional CCD in these children is involved is limited, it is worthwhile considering its role because it may present a pharmacologically treatable form of CCD.

Functional CCD of inherited nature

Protein kinase disorders

Recently a missense mutation (R531G) and another constitutively active mutation (T172D) in the *PRKAG2* gene have been described in patients with WPW syndrome [70]. In contrast to the R302Q mutation in the *PRKAG2* gene (see above) [69], carriers of these two mutations did not have cardiac hypertrophy but did have sinoatrial or atrioventricular block [70]. Because these mutations occur in the gene encoding the $\gamma 2$ regulatory subunit of AMP-activated protein kinase, they may have an effect on cardiac conduction by affecting the phosphorylation state of several cardiac ion channels [71], as has been shown for the T172D mutation. This mutation affected the inactivation properties of the human cardiac sodium channel in a cell expression model. In addition, AMPK has been shown to be a modifier of other human ion channels besides the cardiac sodium channel [71].

Fatty acid oxidation disorders

Fatty acid oxidation disorders are inborn errors of metabolism that affect normal transport and metabolism of fatty acids due to enzymatic defects [72]. The heart is one of the organs that may be affected and cardiomyopathy with conduction and rhythm abnormalities may be one of the presenting symptoms [73,74]. Fatty acid oxidation disorders can also present as conduction disease and atrial arrhythmias, without structural heart disease. Usually these patients have defects in enzymes that regulate mitochondrial transport of long-chain fatty acids (carnitine palmitoyl transferase type II, carnitine-acylcarnitine translocase) [72—74].

The pathophysiology of conduction disease and other clinical features in fatty acid oxidation disorders, results from accumulation of fatty acid metabolites downstream from the enzyme defect [73]. The long chain fatty acid metabolites accumulating in these enzyme defects may be toxic to myocytes, but additionally they may affect ion channel proteins. They have been shown to reduce the inward rectifying K^+ and depolarizing Na^+ current, to activate Ca^{2+} channels, and to impair gap-junction hemi-channel interaction [73]. With the exception of the effects on Ca^{2+} channels, these alterations negatively affect conduction in the heart. Since multiple types of ion currents are simultaneously affected, they may deliver a substrate for cardiac arrhythmias. These disorders are rare, and probably underestimated, but present a potentially treatable cause of childhood arrhythmias and conduction disease.

The cytoskeleton

Sometimes the first and most prominent symptom of inherited cardiomyopathy or muscular dystrophy is isolated CCD, without or before the development of detectable structural cardiac abnormalities [60,63—67]. It may be speculated that in these cases, mutations in cytoskeletal proteins directly or indirectly, alter ion channel function. Some recent studies that show the association of ion channel and cytoskeletal proteins, support this view. That is, the intracellular located protein γ-syntrophin, associates and interacts with the pore forming α-subunit of the cardiac sodium channel, thereby regulating its membrane expression and gating behaviour [75]. As mentioned previously, this ion channel is vital for normal cardiac conduction. Syntrophin additionally associates with the cell-membrane associated proteins dystrophin and ankyrin, the latter are known to interact with the modulatory β-subunits of rat brain voltage gated sodium channels [75—78]. β-Subunits are small transmembrane proteins that have extracellular regions which interact with extracellular matrix proteins [77]. Disruption of cytoskeletal organization may therefore be involved in abnormalities of cardiac conduction, as much arising from structural as from functional malfunction [79—99]. Inversely, these interactions may additionally explain why in some cases of sodium channel mutations, exaggerated fibrosis is found, probably resulting from abnormal function or expression of sodium channels [36,37]. The role of the cytoskeleton in electrical diseases of the heart was additionally convincingly proven by the identification of a loss-of-function mutation in ankyrin in the long QT syndrome type 4 [10].

Mutations in the *SCN5A* gene

The first and as yet only gene that has been found to play a role in functional familial CCD is *SCN5A*, encoding the α-subunit of the cardiac sodium channel (hH1) [32—44]. In 1999, in one family with progressive CCD and in another with

non-progressive CCD, a causal relationship was found with two different mutations in the *SCN5A* gene [32]. Both these mutations resulted in non-functional human cardiac sodium channels. Carriers of these mutations are thus expected to have only 50% of the normally available sodium channels, namely those encoded by their normal allele. Consequently, a considerable reduction in depolarizing sodium current is to be anticipated, which will give rise to a slowing of conduction. Other mutations in the *SCN5A* gene involved in CCD alter the function of sodium channels. These mutations usually reduce the cardiac sodium current by reduction of their membrane expression, probably through actions of the quality control system in the endoplasmatic reticulum of the cell, or by changing the gating properties of the channel [3].

Presently 11 *SCN5A* mutations have been published that are causally related to inherited cardiac conduction disease [32–44]. Combinations of *SCN5A* mutations and degenerative abnormalities have, however, also been reported and it is likely that such combinations will also be present in ageing *SCN5A* mutation carriers as well [36].

Polymorphisms in the connexin gene

Connexins are the building blocks of gap junction channels that functionally and electrically connect cardiac myocytes [7,9]. They are responsible for coupling and current conduction between neighbour myocytes [7,9]. Presently only one polymorphism in the atrial connexin40 gene has been identified in familial atrial standstill and CCD. These patients additionally carried an *SCN5A* mutation (D1275N) that reduced Na-current [38].

Relationship between pathophysiological mechanism underlying CCD and clinical phenotype

Comparison of the clinical symptoms that accompany structural or functional CCD respectively, reveal some (small) differences that relate to the age of clinical manifestation, the extent of the disease, and the incidence of arrhythmias.

Age of clinical manifestation

Symptoms of structural congenital CCD due to anatomical defects of the heart and the conduction system, such as those found in chromosomal disorders and septation defects due to mutations in transcription factor genes, may already be present in utero or at birth. However, in the great majority of the reports where these defects were found to be causally related to mutations in *PRKAG2*, *NKX2-5* or *LMNA*, the disease is recognized at an adult age (Table 1) [27,30,31,60,63–70]. Presenting symptoms may therefore be due to the structural cardiac abnormalities (e.g. shunting) or due to conduction abnormalities. Symptoms of congenital CCD caused by sclerodegenerative abnormalities, e.g. due to the autoimmune mechanism, are often already present at an early age [49–51,57–59].

Functional congenital CCD, on the other hand, may be incompatible with life or becomes evident early in life (Table 2) [32,33,35,37,38,42,43,44]. However, in one report on CCD associated with a reduction in I_{Na} due to a mutation in *SCN5A*, symptoms of CCD appeared only later in life [36]. On the basis of this report we may speculate that a reduction in available functional sodium channels, and the consequent reduction in I_{Na}, can probably be tolerated to some extent. The effects of a reduction in I_{Na} may therefore sometimes not become evident until a later age, when conduction in the heart becomes impaired because of the naturally occurring ageing process. Interestingly, the normal ageing process usually involves sclerosis, although evidence is emerging that sclerosis is enhanced in carriers of loss-of-function *SCN5A* mutations [36,37].

Extent of the disease

In structural CCD, the conduction abnormalities are often localized in a specific part of the specialized conduction system. Obviously, in CCD associated with chromosomal disorders or mutations in transcription factor genes, conduction problems are limited to the part of the specialized conduction system involved in the septation defect. Symptoms of congenital CCD caused by sclerodegenerative abnormalities, e.g. due to the autoimmune mechanism, are mostly restricted to the AV-nodal region [49–51,57–59]. The only exception, forms the group of DCM due to *LMNA* mutations, in which the atria, the bundle of His, the bundle branches and the working myocardium are affected [60–62].

If we consider the group of purely functional CCD, without structural abnormalities, this group is mainly represented by cases of CCD due to *SCN5A* mutations. Cardiac conduction seems to be more generally impaired in reports where an *SCN5A* mutation is involved. This is to be expected in view of the fact that the cardiac sodium channel is present and functional throughout all regions of the heart. A mouse model with a loss-of-function *SCN5A* mutation, nicely supports this view [82].

Mice homozygous for the mutation display in vivo impaired atrioventricular conduction and preparations of the isolated hearts show impaired atrioventricular, delayed intramyocardial conduction and increased ventricular refractoriness. Besides these abnormalities, ventricular tachycardia due to reentry occurred in the isolated hearts [82].

Cardiac arrhythmias

Because of the limited information and the low number of patients in many of the clinical reports, a statement about the incidence of arrhythmias in relation to structural or functional CCD, is precarious. The occurrence of tachyarrhythmias and sudden cardiac death (SCD), may be expected to be more frequent in patients with CCD that carry loss-of-function *SCN5A* mutations, comparable with patients with *SCN5A*-associated idiopathic VF and Brugada syndrome [3]. Evaluation of Tables 1—3 shows that this difference is not as clear as expected. In the 26 reports on structural CCD (Table 1) SCD is reported 8 times and in 6 cases (dilated) cardiomyopathy is involved. Atrial arrhythmias are reported 10, and ventricular arrhythmias 3 times (Table 1). In the 11 reports on CCD in the presence of an *SCN5A* mutation (Table 2) SCD is reported twice and ventricular arrhythmias 3 times. Among the 16 reports of congenital CDD of unknown cause (Table 3), SCD is reported 6 times, of which 5 times due to complete heart block. In this group atrial or ventricular arrhythmia (broad complex tachycardia of unknown origin) is reported once. Thus, from these numbers cardiac arrhythmias do not seem to be more frequent among patients with functional CCD due to *SCN5A* mutations.

Conclusions

In congenital CCD there are two pathophysiological pathways, a structural and a functional. Each pathway can be further divided in inherited, congenital or acquired pathophysiological mechanisms (Fig. 2). Structural and functional CCD are two mechanistically different diseases which may however have some overlap. Reduced sodium current due to mutations in the *SCN5A* gene, encoding the cardiac sodium channel, is the most important mechanism in congenital CCD without structural abnormalities and may already be symptomatic at an early age. Additionally, this mechanism may be involved in congenital CCD associated with abnormalities of the cytoskeleton of the heart [60,68].

More detailed knowledge of the function of the cardiac sodium channel, by studying inherited electrical disorders like congenital CCD, may enable us to develop a pharmacological treatment for this form of congenital CCD. Additionally it may enable us to develop drugs to treat other cardiac diseases that are caused by loss-of-function *SCN5A* mutations. Until then, the treatment for *SCN5A* related CCD is pacemaker implantation, as in other forms of CCD. Due to the fact that the whole myocardium may be affected in *SCN5A* related CCD, pacemaker treatment may, however, be less successful in these circumstances [33].

Hence, for both treatment and scientific purposes, an accurate, genetic diagnosis in inherited CCD is important.

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