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REVIEW

Uncommon Cardiomyopathies

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Abbreviations
α-Gal A = α-galactosidase A
ACE = angiotensin converting enzyme
AFD = Anderson-Fabry disease
AV = atrioventricular
BBB = bundle branch block
DCM = (idiopathic) dilated cardiomyopathy
ECG = electrocardiogram
ERT = enzyme replacement therapy
Gb3 = globotriasylceramide
HCM = idiopathic hypertrophic cardiomyopathy
ICD = implantable cardioverter defibrillator
IVNC = isolated ventricular non-compaction
LSD = lysosomal storage disease
LV = left ventricle
LVEDD = left ventricular end-diastolic diameter
LVH = left ventricular hypertrophy
MRI = magnetic resonance imaging
NYHA = New York Heart Association
PET = positron emission tomography
RV = right ventricle
SRI = strain-rate imaging
TDI = tissue Doppler imaging
TIA = transient ischemic attack
WHO = World Health Organization

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ABSTRACT

Anderson-Fabry Disease (AFD) is an X-linked recessive lysosomal disorder, leading to multisystemic disease because of abnormal glycosphyngolipids widespread accumulation, the result of α-galactosidaseA deficient activity. Cardiac involvement is common; includes left ventricular hypertrophy and gradually impairing cardiac function. Although the disease is unveiled in childhood and culminates in cardiac, cerebrovascular and end-stage renal disease, diagnosis is often delayed or missed. Recently established enzyme replacement therapy (ERT) may improve most of the disease's manifestations. Early diagnosis is thus crucial for AFD patient management.

Isolated non-compaction of the ventricular myocardium (IVNC) is a rare congenital form of cardiomyopathy. It is characterized by the postnatal persistence of the embryonic pattern of myoarchitecture, consistent of prominent trabeculations and deep intertrabecular recesses, and assumed to occur as a consequence of intrauterine arrest of myocardial compaction. Contemporary diagnosis has been facilitated by the introduction of specific morphologic criteria by echocardiography and magnetic resonance imaging. Management issues revolve around the management of heart failure, arrhythmias and thromboembolic events in order to prevent the significant morbidity and even mortality that has been associated with this entity. Significant overlapping with many other forms of cardiomyopathies suggest that non-compaction may be a morphologic trait rather than a distinct cardiomyopathy.

INTRODUCTION

Inherited cardiomyopathies are infrequent myocardial disorders, compared to ischemic, valvular or hypertensive heart disease. Among them, there are really rare diseases, which "deserve" to be referred to under the term "rare or uncommon cardiomyopathies". Two of these cardiomyopathies will be described in this review.

FABRY CARDIOMYOPATHY

Anderson-Fabry disease (AFD, synonym Fabry disease) is an X-linked lysosomal storage disease (LSD) caused by mutation in the gene encoding the lysosomal enzyme α-galactosidase A (α-Gal A). The resultant deficiency in α-Gal A activity leads to

intra-lysosomal accumulation ("vacuolization") of neutral glycosphingolipids, mainly globotriasylceramide (Gb3), in various organ systems.

AFD is a rare, panethnic disorder; incidence has been estimated at 1 in 40.000 to 1 in 117.000 live births for males.[1] However, over the last decade, scientific evidence based on patient cohorts with unexplained left ventricular hypertrophy (LVH), thought to be due to sarcomeric hypertrophic cardiomyopathy (HCM), identified 7% of males[2] and 12% of females[3] with either biochemical or genetic evidence for Fabry disease. The heightened cardiological interest was to be expected as the probable AFD population expanded.

CLINICAL PRESENTATION

As mentioned above, the pathophysiological mechanism of AFD is the Gb-3 abnormal accumulation ("vacuolization") in lysosomes of vascular endothelium and smooth muscle cells of blood vessels, in gaglion cells, in many cell types in the heart, kidneys, eyes and most other tissues. That leads to a complex and multisystemic disorder, with symptoms starting early in life.[1]

During childhood, the clinical onset typically occurs with acute, mostly burning pain in the extremities ("acroparesthesiae") or in any region of the body, due to stored sphingolipids in the dermal axons. Some complain about neck pain and headache (not always distinguishable from migraine or cluster headaches). Physical activity, high temperature, foods (coffee, meat), alcohol, emotional stress can trigger the pain, not responding to common painkillers. Chronic pain has been described as the most debilitating symptom in patients with AFD. Additional symptoms include heat/cold intolerance, recurrent fever, and hypohidrosis (due to impaired sympathetic innervation of the skin and sweat glands dysfunction from deposition of storage material). Corneal opacities (corneal verticillata) have been described as almost pathognomonic for AFD (occur in 75% in female and up to 90% in male patients) and do not affect the vision ("Fabry cataract"). The diagnosis is only made by split-lamp examination.

During adolescence, the classic angiokeratoma appears. It is a pinhead sized, reddish-purple maculopapular skin lesion ('rush'), not disappearing with pressure. Typical locations are the fingertips, the bathing trunk area, the buttocks, the periumbilical area, but may also occur on the mucosa (on the lips or anywhere in the gastrointestinal tract) (Fig. 1). **In adulthood,** renal dysfunction, cerebrovascular complications and cardiac disease are already apparent.

Although proteinouria (regarded as the earliest sign of clinically relevant renal involvement in AFD) is presented from the second decade of life, by age 47, half of all untreated patients have already developed terminal renal failure. Renal biopsies in children have shown that lipid storage in podocytes and glomerular, interstitial or vascular changes develop even before clinical renal functional impairment occurs. Relative to central nervous system, the most severe complication in AFD are transient ischemic attacks (TIA) and stroke. Almost 25% of patients experience a cerebrovascular event over the course of their disease (mean age 34 years in men, 54 years in women).

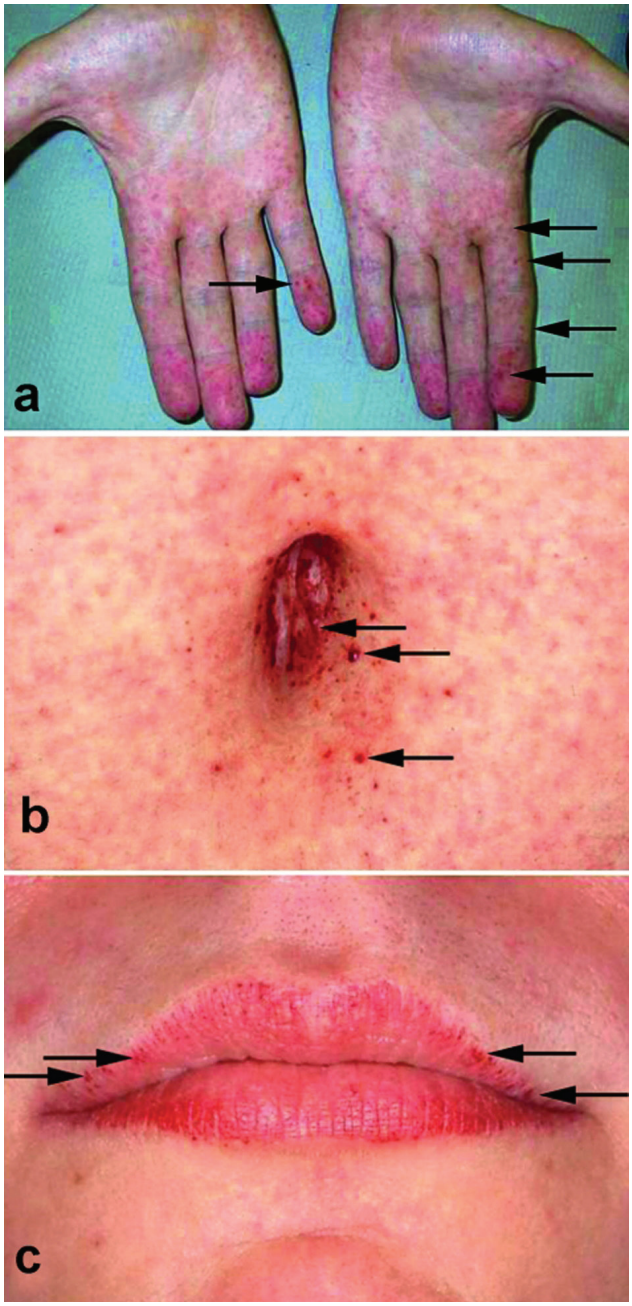

FIGURE 1. Angiokeratoma a) on the hands; b) periumbilically; c) on the lips [Beck M: "Fabry disease, 2nd ed. 2007"].

CARDIAC INVOLVEMENT

Cardiac involvement is common but variable and clinical severity increases with increasing age. On average, more than 50% of patients with AFD have cardiac symptoms at the age of 36. Myocardial Gb3 deposits (in myocytes, conduction system, vascular endothelium, valve tissue) represent 1-2% of the total cardiac mass.[4] Therefore, it is likely that disease in the heart results from activation of other signaling pathways (inflammation, neuron-hormonal dysregulation) that lead to hypertrophy, apoptosis, necrosis and fibrosis. Myocardial ischemia in the absence of significant disease of epicardial arteries and substantial fibrosis are major determinants of cardiac remodeling in AFD and contribute to disease progression.

a. Cardiomyopathy. Most patients (male and female) with AFD develop LVH. Early disease is characterized by concentric remodeling, progressing later to concentric hypertrophy. Asymmetric septal hypertrophy, indistinguishable from that seen in sarcomeric cardiomyopathies (dynamic LV outflow obstruction may be seen) accounts for only 5% of cases[2,4,5] The right ventricle may also be affected. LV systolic function seems to be preserved, when conventional methods are used for estimation.[4] Nonetheless, studies using tissue Doppler imaging (TDI) and strain-rate imaging (SRI) have demonstrated reductions in systolic performance, occurring earlier in the longitudinal than in the radial dimension.[6] It seems that early functional abnormalities can be detected using advanced echocardiographic techniques prior to the development of morphological changes (LVH or fibrosis).[6a] Early diagnosis might enable the optimal therapy initiation.[6b] Mild diastolic dysfunction is a common feature of AFD, although restrictive pathophysiology may be identified in the most advanced stages of the disease associated with pronounced fibrosis.[4]

Some authors focused on the recognition of AFD from other forms of LVH by non-invasive imaging hallmarks. Thus, Pieroni et al compared echocardiographic features of patients with AFD, sarcomeric HCM, LVH secondary to hypertension and normal control subjects.[7] He identified thus a specific echocardiographic feature of AFD, reflecting the peculiar pathological substrate of the disease observed at histology and ultrastructural analysis of endomyocardial biopsy tissue. Ultrasound examination in AFD patients revealed a binary appearance of LV endocardial border, systematically absent in HCM and hypertensive patients as well as in normal control patients, thereby resulting in a distinguished echocardiographic feature with a sensitivity and specificity of 94% and 100% respectively, suggesting that binary appearance is an ideal discriminator of AFD from hypertophic cardiomyopathy (HCM), thus an ideal non-invasive diagnostic hallmark of Fabry cardiomyopathy (Fig. 2). Taking it further, other authors with the same study design,[8] anticipated that the binary appearance is likely to be affected by image quality, gain settings and imaging software, making the conclusion that this specific echo-sign is poorly reproducible and lacks sensitivity and specificity (35% and 79% respectively in their own study) to be used as an echo-

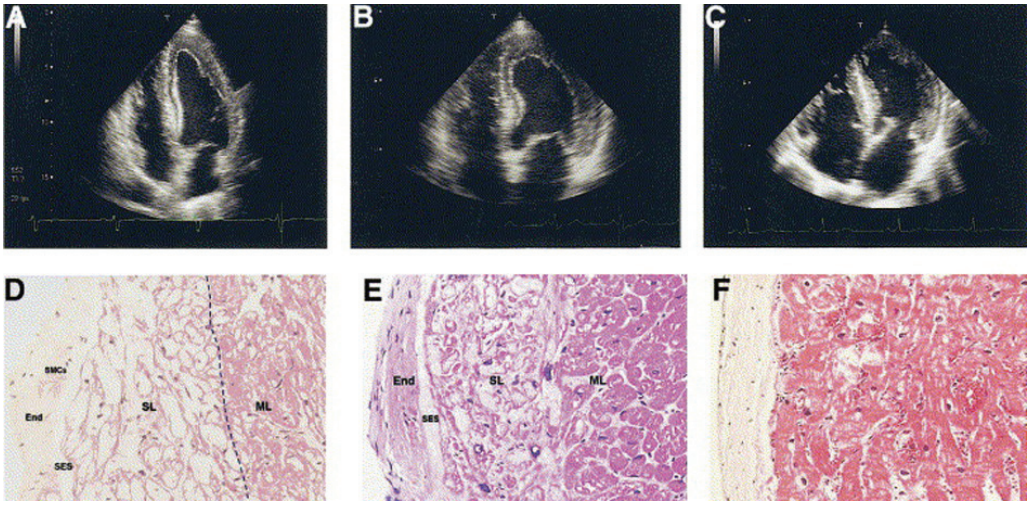

FIGURE 2. Two-dimensional echocardiography in 4-chamber apical view and LV endomyocardial biopsy from two patients with AFD (A, D and B, E) and a patient with sarcomeric HCM (C, F). Comparison of the three echocardiographic frames reveals the presence of a binary appearance of LV endocardial border in the two AFD patients (A, B). This echocardiographic finding reflects the glycosphingolipids compartmentalization involving a thickened endocardium (End) with enlarged and engulfed smooth muscle cells (SMC), a subendocardial empty space (SES), and a prominent involvement of subendocardial myocardial layer (SL), while the middle layer (ML) appears partially spare (D, E). The echocardiographic pattern is absent in HCM (C), despite a similar thickening of the endocardium (F) [Pieroni et al, JACC 2006;47:1663-1671] (permission granted). AFD = Anderson-Fabry disease; HCM = hypertophic cardiomyopathy; LV = left ventric-cle(-ular).

cardiographic screening tool for AFD.

In that direction, cardiac MRI could be used as discriminator of AFD from HCM. In MRI studies, patients with Fabry's related LVH showed LV delayed-enhancement with a typical and consistently founded pattern, characterized by the involvement of the inferolateral basal or mid basal segments and a mesocardial distribution spared the subendocardium.[9] The pattern seems to be specific to AFD; in fact, patients with symmetric sarcomeric HCM had variable locations and distributions of delayed enhancement, mainly in interventricular septum and papillary muscles.[10]

b. Valvular disease in AFD is caused by infiltrating changes within valvular fibroblasts. Left heart valves are most frequently affected, although pulmonary valve involvement is also reported. Typically, valves are thickened and distorted, resulting in mild-to-moderate regurgitation; severe disease requiring surgical operation is infrequent. Aortic root dilatation resulting to aortic valve insufficiency is may be seen.

c. Myocardial ischemia: Although the incidence of myocardial infarction is low in AFD patients, angina pectoris and chest pain are frequent, particularly in patients with LVH. Studies using positron emission tomography (PET) have shown that patients with AFD and angiographically normal epicardial coronary arteries have reduced coronary flow reserve, suggesting that microvascular dysfunction may be responsible for exertional symptoms.[11]

d. Electrophysiological abnormalities: Resting ECG is almost always abnormal (Fig. 3) Voltage criteria for LVH and repolarization changes are the most common abnormalities. Many patients have a short PR interval probably caused by accelerated AV conduction due to nodal Gb3 infiltration. With disease progression, patients develop bundle branch block, AV conduction delay and progressive sinus node dysfunction, requiring pacemaker implantation.[12] Supraventricular tachycardias, atrial fibrillation and flutter are frequently observed,[12] although individual cases of fatal malignant arrhythmias requiring implantable cardioverter defibrillator (ICD) implantation are also reported.

DISEASE PHENOTYPES-DIAGNOSIS

The disease is classified into two major phenotypes according to the onset of clinical symptoms and the absence or presence of residual α-Gal A activity.

The early onset (or classic type) characterized by early manifestation of the multi-systemic disorder, while cardiac involvement is appears later in life. Males with classic disease

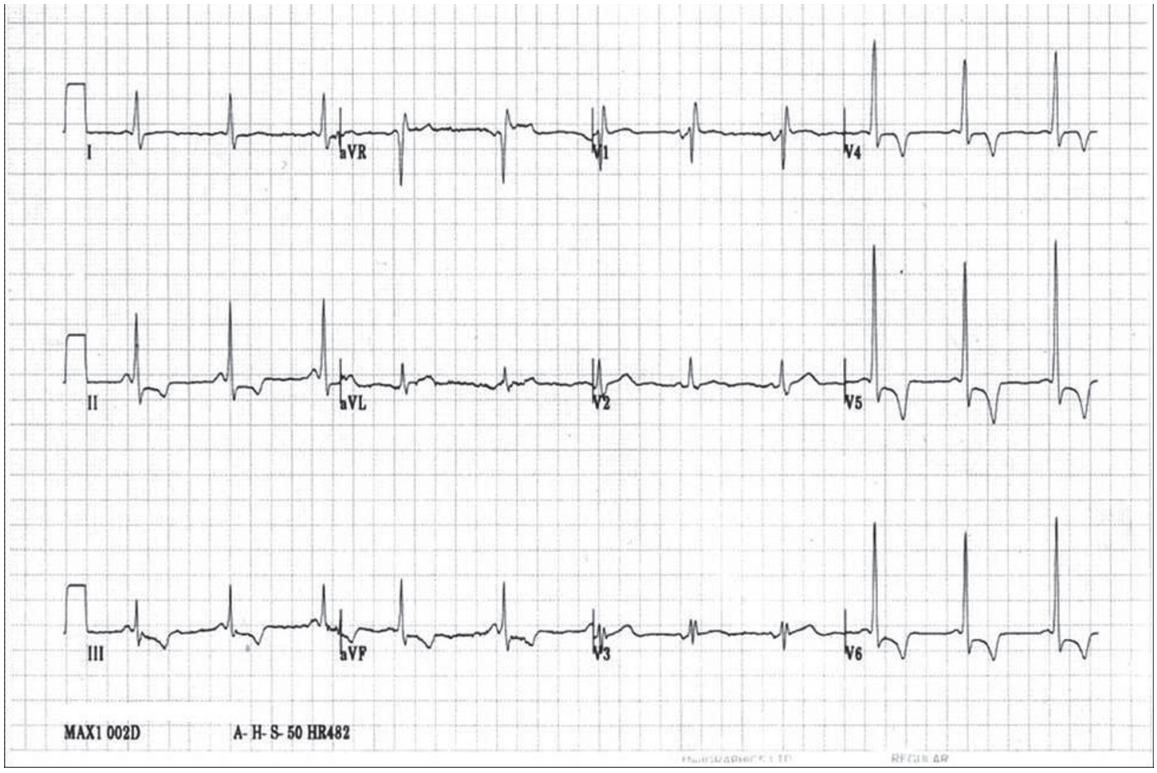

FIGURE 3. ECG showing left ventricular hypertrophy (LVH), repolarization abnormalities and short PR interval in AFD. AFD = Anderson-Fabry disease

have no or very low α-Gal A activity and the diagnosis is easily made by determining that in plasma or peripheral leukocytes. Tissue biopsy may also establish the diagnosis, revealing the typical "vacuoles" by electron microscopy.

The late onset (atypical form or cardiac/renal variant) patients are usually asymptomatic until their late thirties, and their clinical manifestations are then limited to the heart/kidneys. These male patients have some residual plasma enzymatic activity and biochemical diagnosis is possible, but tissue biopsy is pathognomonic when targeting into heart/kidney and not throughout the body.[2,13]

Although AFD has been considered an X-linked recessive disorder, affected women are increasingly recognized[3] (with clinical status ranging from asymptomatic to full-blown disease as severe as that in affected males), suggesting that the disease follows an X-linked-dominant rather than –recessive transmission. The variability in females may be partly accounted for by a nonrandom or skewed inactivation of the wild type X-chromosome, but other factors such as genetic modifiers may play a role. Women carriers can have normal to very low α-Gal A activity; therefore their specific family mutation in the α-Gal A gene must be demonstrated for the diagnosis to be made. Tissue biopsy is diagnostic, when targeting to the affected organ.

Prenatal diagnosis can be made by demonstration of an XY karyotype and deficient α-Gal A activity in cultured amniocytes or chorionic villi.[14] If the family's mutation is known, molecular studies can replace or confirm the enzymatic diagnosis.

In conclusion, the clinical course of AFD is heterogeneous and variable. The range of possible differential diagnoses is broad and concerns many medical (overlapping) subspecialties. The risk of a delayed or incorrect diagnosis is probably high. The time period of symptoms onset to the correct diagnosis is long:[1] 13 years in men and 17 years in women!

PROGNOSIS

Progressive renal failure, cardiomyopathy and myocardial infarction, as well as TIAs and strokes reduce the survival time for male untreated patients with AFD to an average of 55 years, for women to 70 years.[15,16] The quality of life is obviously reduced compared with the normal population.[1] A multisystemic disease that is accompanied by chronic pain, that has a far too long diagnostic latency period and a substantially lower life expectancy is necessarily also accompanied by an increased risk of depression.

THERAPY

Until 2001, treatment for AFD patients was only symptomatic. Patients with chest pain should receive conventional anti-aginal treatment, like β-blockers (with the provision that medicines may aggravate the tendency of some patients to symptomatic bradycardia and AV conduction block) or dihydropyridine calcium channel blockers (relatively effective and safe), while antiplatelet treatment should be offered to all symptomatic patients. Angiotensin converting enzyme (ACE) inhibitors and diuretics should be used in patients with evidence for systolic impairment, while patients with advanced congestive heart failure may be candidates for heart transplantation (the intrinsic enzyme production within the graft should prevent reoccurrence of disease). Pacemaker implantation may be required for conduction abnormalities or ICD implantation for malignant arrhythmias. ACE inhibitors should be considered in any patient with proteinouria or renal insufficiency.

Since 2001, enzyme replacement therapy (ERT) is available. Two preparations have been licensed for the causal treatment of AFD in Europe, both are gene technologically produced α-Gal A variants based on human DNA, administered periodically as infusions. The treatment is entirely safe (allergic reactions, headache, flushing, raised temperature, chills, nausea and vomiting may occur) and has to be continued for lifelong. The cost amounts to 250 000 euros per patient per year!

Several studies have shown that ERT is effective in quality of life reducing symptoms (pain,[17] angina pectoris,[18] gastrointestinal[19] and sweating disturbances), in cardiac involvement (regression or no progression of LVH,[20] improvement of systolic performance indices[6]), as well as in renal failure (dissolving Gb3 storage in glomeruli leading to improvement in creatinine clearance[17,18]). Obviously, it has been possible for only very few studies to be conducted in a double blind, randomized and controlled fashion, as patients with a known diagnosis of AFD were given causal therapy after the preparations had become licensed. The available information about the long term treatment with ERT comes mostly from cohort studies that were developed from the two available patient registries, or from open extension studies of the phase III trials. Nonetheless, it is clear that patients with AFD benefit from ERT. It seems that ERT initiation in the early phases of the disease would be more effective than waiting until measurable organ damage develops. However, even 9 years after ERT has been introduced, many therapeutic questions remain unresolved- for example, whether the treatment is able to prevent relevant organ manifestations and reduce mortality due to AFD.

CONCLUSION

AFD is an important differential diagnosis in middle aged and elderly patients with unexplained LVH. Emerging evidence suggests that ERT substantially improves many of

the features of that malignant disease, including some aspects of cardiac involvement. Thus, correct and early diagnosis dramatically improves the prognosis of AFD patients.

ISOLATED VENTRICULAR NON-COMPACTION

Noncompacted myocardium is a rare myocardial disorder, with prevalence estimated 0.014% of patients referred for echocardiography.[1] The phenotype resembles "persistent intramyocardial sinusoids", a well-known cardiac anomaly among pediatric cardiologists. However, the latter are associated with congenital obstructive lesions of the right or left ventricular outflow tract, such as pulmonary[22] or aortic[23] atresia with intact ventricular septum. In these patients, regression of the embryogenic sinusoids is impaired during ontogenesis by ventricular pressure overload that results in deep recesses that communicate with both the ventricular cavity and the coronary artery system.

By contrast, isolated ventricular noncompaction (IVNC) is defined as idiopathic cardiomyopathy characterized by an altered structure of the myocardial wall (consistent by prominent trabeculations and deep intratrabecular recesses), as a result of intrauterine arrest of compaction of the myocardial fibers, in the absence of any coexisting congenital lesion.[24,25]

Since the first reported case of IVNC in 1986[26] and a more extensive description in 1990,[24] case reports[27-29] and a few studies in paediatric[30,31] and adult populations[25,32-35] have been published. However, IVNC remains an unclassified cardiomyopathy according to WHO classifications of cardiomyopathies.[36,37]

PATHOGENESIS

In the early embryo, the heart is a loose interwoven mesh of muscle fibers.[38] During the first six weeks of fetal life, before the development of the coronary circulation, the human LV endocardium consists of a spongy meshwork of abundant fine trabeculae with deep intertrabecular recesses, which serve to increase myocardial oxygenation. At 12 weeks, when ventricular septation is complete, the trabeculae start to solidify at their basal area contributing to added thickness of the compacted myocardial layer. The large spaces within the trabecular meshwork flatten or disappear. Compaction of the ventricle progress from the epicardium to the endocardium and from the base of the heart to its apex, is a process more complete in the left than the right ventricle and is finally completed in the early fetal period.[39] Although the cause of IVNC is not fully elucidated, it is believed to represent an arrest in endomyocardial morphogenesis[24] to embryonic phase, with prominent trabeculations and deep intertrabecular recesses (Fig. 4).

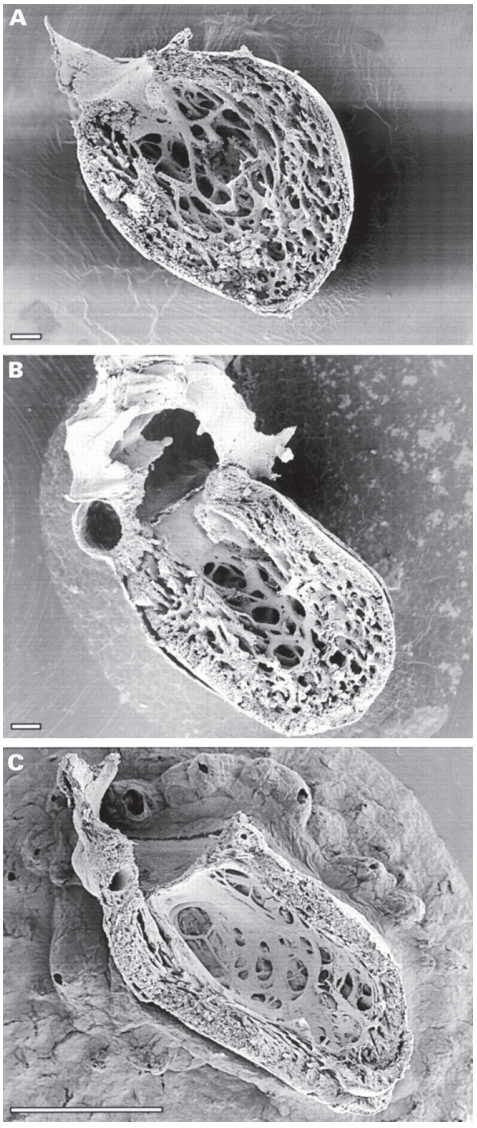

FIGURE 4. The process of normal trabecular compaction. (A) at first six weeks of fetal life, (B) at 12 weeks and (C) completion of myocardial compaction. [Sedmera et al, Anat Rec 2000;258:319-337].

DIAGNOSIS

The defining characteristic of IVNC is trabeculations. However, prominent trabeculations (identified as discrete muscle bundles, more than 2 mm in diameter, that stand over the background of the LV endocardium) are considered to be common variant of the normal human heart[40] or secondary to various cardiac diseases, developed after pathologic changes in the ventricular wall structure and cavity geometry.[41] Therefore, IVNC diagnostic criteria were necessary, in order to differentiate from other cardiac over-trabeculation conditions and normal variants.

Three methods of criteria have ever proposed, based mainly on echocardiography:

A. CHIN CRITERIA[24]

These focus on trabeculae at the LV apex. IVNC is defined by a ratio of X/Y≤0.5, where X: the distance from the epicardial surface to the trough of the trabecular recess, and Y: the distance from the epicardial surface to peak of trabeculation. Measures obtained on the parasternal short axis and apical views, at end-diastole (Fig. 5).

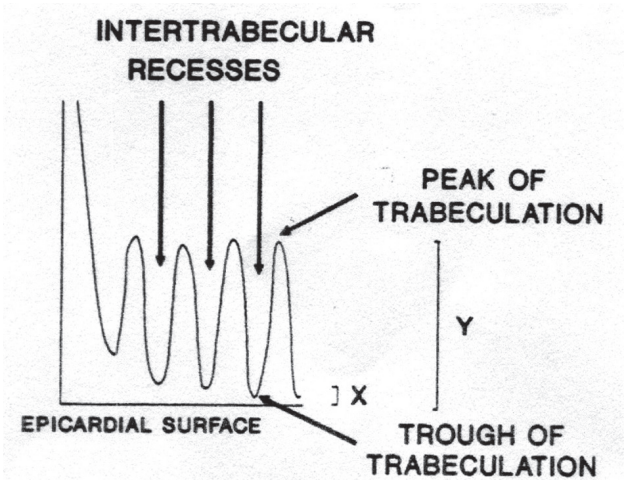

FIGURE 5. X/Y ratio calculation. X: the distance from the epicardial surface to the trough of the trabecular recess, Y: the distance from the epicardial surface to peak of trabeculation. [Chin et al, Circulation 1990;82:507-513] (permission granted).

B. JENNI CRITERIA[42]

1. Absence of co-existing cardiac structural abnormalities.
2. A two-layer structure, with thin epicardial compacted layer (C) and a thick endocardial non-compacted layer (N), consisted with numerous, excessively prominent trabeculations and deep intertrabecular recesses, where a ratio N/C>2 identifies IVNC (Fig. 6).
3. Affected segments (trabeculated) are typically located in apex and mid-ventricular inferior/lateral wall.
4. Recesses supplied by intraventricular blood on color Doppler.

Measures obtained on parasternal short axis, at end-systole.

C. STOLLBERGER CRITERIA[33]

1. More than 3 trabeculations protruding from the LV wall, apically to the papillary muscles, visible in a single imaging plane, confirmed by echocardiography, MRI or computed tomography.
2. Intertrabecular spaces perfused from the ventricular cavity, visualized on color Doppler.

The Chin et al criteria were the first diagnostic template, however eventually abandoned due to practical implications. The Stollberger et al criteria never gained general acceptance. Nowadays, the Jenni et al criteria are the most widely used, and although some of them are occasionally found in other heart diseases, their combination appears highly specific for IVNC diagnosis (specificity ≥95%).[41]

Apart from the pattern, location and extension of the trabeculations, the affected segments are typically hypokinetic, but hypokinesia may extend to morphologically unaffected

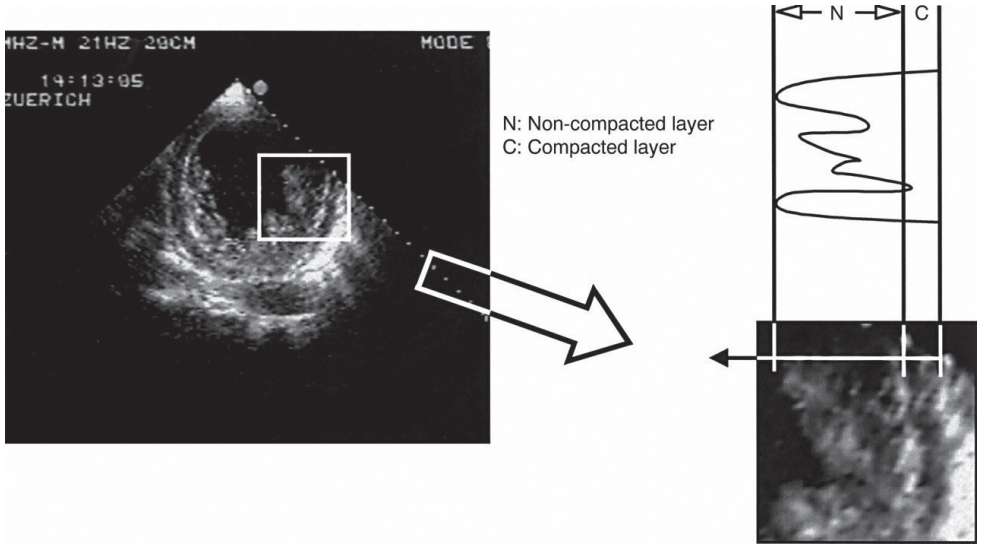

FIGURE 6. N/C ratio calculation. N: non-compacted, C: compacted LV wall segment. [Jenni et al, Heart 2001;86:666-671] (permission granted).

segments, resulting in a decreased LV ejection fraction. Left atrium is usually dilated. The right ventricle (RV) may be affected[25] (up to 40%), although diagnostically challenging because normal RV structure is also trabeculated. Therefore, the diagnostic contribution of RV morphology is rather qualitative. Isolated RVNC has not reported so far. Diastolic dysfunction is common, usually reflecting impaired LV relaxation and in rare cases of severe disease demonstrates restrictive physiology.

Thus, echocardiography has been the diagnostic procedure of choice, but the diagnosis is often missed because of the limitations of poor quality or near field imaging. In such cases, echo contrast imaging is strongly recommended in suboptimal studies, as it improves the endocardial border definition, allowing a better delineation of the trabeculae and deep recesses filled by microbubbles.[43] On the other hand, overestimation of myocardial trabeculations by 2D echocardiography (off-axis apical or short-axis planes) is often made, leading to over-diagnosis of the disease by common criteria. As recently published,[43a] 3D echocardiography allows for an accurate measurement of the extent of noncompacted myocardium, due to its high spatial resolution and accuracy in volumetric quantification. It is, thus, superior to 2D echocardiography for the identification of pts with IVNC.

The role of cardiac MRI in IVNC diagnosis is critical, when echocardiographic windows are limited or when echocardiography cannot distinguish reliably between IVNC and other cardiac pathology such as apical hypertrophy, endomyocardial fibroelastosis, metastatic disease or apical thrombus. Following echocardiographic criteria, MRI criteria for IVNC diagnosis[44] demand a ratio N/C >2.3, where N=non-compacted and C=compacted segment, measured at end-diastole. Left heart catheterization is not considered a first line diagnostic modality for IVNC diagnosis but rather helps exclude coronary artery disease as the cause of LV dysfunction.

CLINICAL PRESENTATION

Three major clinical manifestations of IVNC have been described: heart failure, arrhythmias and thromboembolic events. Findings vary among patients, ranging from asymptomatic individuals identified by IVNC family screening, to disabling congestive heart failure patients. In a series of 65 patients with IVNC,[35] heart failure (including NYHA class III-IV) presented in 83% of patients, palpitations in 6%, syncope in 4%, chest pain in 4% and sustained ventricular arrhythmia in 2%. When diagnosis was non-symptom based, familial referral was the main reason in 59% of patients, ECG abnormalities in 23%, referral for "tricky" echocardiographic imaging in 12%, cardiac murmur in 5%. ECG is usually abnormal in IVNC (mostly presenting non specific repolarization abnormalities, and BBBs, but cases of ventricular pre-excitation have been reported[45]). Dysmorphic facial appearance has been also reported (represented by prominent forehead, bilateral strabismus, low-set ears, micrognathia), but only in pediatric populations.[24,30,31] Arrhythmias are the main reason for concern in IVNC patients. Both supraventricular and ventricular tachyarrhythmias have been reported.[24,25,32] It is hypothesized that due to fibrosis of the trabeculations and subendocardial ischemia, patients with IVNC are more prone to ventricular arrhythmias. Sudden cardiac death is a significant risk in these patients, with an incidence of 13-18% in some series.[21,32,33] Systemic thromboembolic complications can be a serious source of morbidity: cerebrovascular accidents, TIAs, and mesenteric infarction have been described.[24,32] It seems that the excessively trabeculated noncompacted myocardium sets the ideal ground for thrombus formation. Paroxysmal atrial fibrillation and systolic dysfunction are additional proposed mechanisms for thromboembolism in IVNC.

GENETICS

The studies looking into the genetics of IVNC suggest significant heterogeneity in the genetic substrate for this disorder. According to one report, up to 50% of infantile[24] and up to 18% of adult cases[32] of IVNC are familial, with the remainder being sporadic. Both X-linked as well as autosomal transmission has been observed. In the former, mutations of the TAZ (G4.5) gene located in the Xq28 region cause IVNC associated with other neuromuscular disorders[46] and affect male offspring (X-linked recessive). The majority of cases causing familial clustering in adults are not X-linked but rather transmitted in an autosomal dominant manner.[47] Several genes or chromosomal loci have been identified. Of these, mutations to the 11p15locus[48] (gene unidentified) and to the Cypher/ZASP[49] lead to isolated non-compaction or DCM, whereas mutations in the CSX or the DTNA[46] genes are usually cause other congenital heart diseases in addition to non-compaction. It is, thus, difficult to make specific recommendations for genetic screening in patients identified as having IVNC. The prognostic significance of identifying any of the aforementioned genetic mutations is not clear. A detailed family history (focusing on sudden cardiac death, cardiomyopathies, heart failure and arrhythmias) is mandatory in all patients. Further genetic testing would be of interest in those with a positive family history. Echocardiographic imaging of first-degree relatives is well justified.

THERAPY

There is no specific therapy for IVNC. Treatment is focused on the 3 major clinical manifestations: heart failure, arrhythmias and systemic embolic events. Patients with reduced systolic function should be treated with standard medication

(ACE-inhibitors, diuretics, carvedilol). The indications for biventricular pacing are similar to the criteria employed for dilated cardiomyopathy. Heart transplantation should be considered for patients with IVNC who have end-stage heart failure. Holter monitoring should be considered once a year to detect asymptomatic arrhythmias. The indication for ICD therapy should be similar to those in dilated cardiomyopathy.

Prevention of embolic complication is crucial. Although early studies recommended anticoagulation for all patients with IVNC as soon as the diagnosis has been made, independent of ventricular function, to prevent embolic events,[32] recent studies suggested that non-compaction itself is not thrombogenic[50,51] and anticoagulation may be administered according to current recommendations (significant systolic dysfunction, atrial fibrillation and prior embolic events).

PROGNOSIS

Early reports of the disease generally attached a very poor prognosis, in highly symptomatic patients affected by heart failure, sustained ventricular tachycardias or thromboembolic complications.[24,30,32] Subsequent studies progressively broadened our picture of the affected population, extending it to patients with less and less severe disease.[34-35a] Generally, the prognosis is not favorable. Progressive systolic dysfunction, arrhythmias and even sudden death are the major causes for morbidity and mortality, especially in symptomatic patients. Asymptomatic patients may have better prognosis, a delayed progression with less complications. Poor prognostic markers include the development of atrial fibrillation, bundle branch block, LV end-diastolic dimension >60 mm and NYHA class III-IV.[32]

CURRENT STATUS

The new millennium "enthousiasm" has suggested IVNC as the 5th cardiomyopathy,[42,52] in following classifications. The initial optimism shrunk as several studies highlighted the overlapping phenotype of familial IVNC with that of familial DCM and suggested that IVNC could be classified as a sub-type or variant of idiopathic DCM rather than a distinct cardiomyopathy in itself.[34] Further studies demonstrated that IVNC phenotype can overlap with many other forms of cardiomyopathies (in addition to the DCM), like hypertrophic and restrictive cardiomyopathies, suggesting that IVNC is a morphologic trait rather than a distinct cardiomyopathy.[53] In a recent study,[54] designed to determine the proportion of patients fulfilling IVNC criteria in an adult population referred to a heart failure clinic, an unexpectedly high percentage identified as IVNC patients (78.7%, 63.8% and 53.8% of patients, according to Chin,[24] Jenni[42] and Stollberger[33] criteria respectively). The interpretation of the finding is that either IVNC is a quite frequent cardiac disease, or current criteria are too sensitive!

CONCLUSION

Although in the USA IVNC is already classified as a primary genetic cardiomyopathy by the AHA,[36] in Europe it still remains an unclassified one.[37] It seems that there are still many controversies concerning diagnostic templates, nomenclature, prognosis and the necessity to classify IVNC as a distinct entity, rather demand a new nosographic definition.[55,56]

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