

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Circulation 2010, 121:2169-2175: originally published online May 10, 2010
doi: 10.1161/CIRCULATIONAHA.109.929646

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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Peripartum Cardiomyopathy as a Part of Familial Dilated Cardiomyopathy

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Background—Anecdotal cases of familial clustering of peripartum cardiomyopathy (PPCM) and familial occurrences of PPCM and idiopathic dilated cardiomyopathy (DCM) together have been observed, suggesting that genetic factors play a role in the pathogenesis of PPCM. We hypothesized that some cases of PPCM are part of the spectrum of familial DCM, presenting in the peripartum period.

Methods and Results—We reviewed our database of 90 DCM families, focusing specifically on the presence of PPCM patients. Then, in a reverse approach, we reviewed 10 PPCM patients seen in our clinic since the early 1990s and performed cardiological screening of the first-degree relatives of 3 PPCM patients who did not show a full recovery. Finally, we analyzed the genes known to be most commonly involved in DCM in the PPCM patients. We identified a substantial number (5 of 90, 6%) of DCM families with PPCM patients. Second, cardiological screening of first-degree relatives of 3 PPCM patients who did not show full recovery revealed undiagnosed DCM in all 3 families. Finally, genetic analyses revealed a mutation (c.149A>G, p.Gln50Arg) in the gene encoding cardiac troponin C (*TNNC1*) segregating with disease in a DCM family with a member with PPCM, supporting the genetic nature of disease in this case.

Conclusions—Our findings strongly suggest that a subset of PPCM is an initial manifestation of familial DCM. This may have important implications for cardiological screening in such families. (*Circulation*. 2010;121:2169-2175.)

Key Words: cardiomyopathy ■ genetics ■ pregnancy

Peripartum cardiomyopathy (PPCM) is a rare, life-threatening cardiomyopathy that affects women late in pregnancy or in the early puerperium. Diagnostic criteria for PPCM are (1) development of cardiac failure in the last month of pregnancy or within 5 months after delivery, (2) left ventricular systolic dysfunction (left ventricular ejection fraction <45%), (3) no identifiable cause for cardiac failure, and (4) no recognized heart disease before the last month of pregnancy.¹⁻³

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A number of risk factors for PPCM have been identified, including advanced maternal age, multiparity, and eclampsia. In addition, several possible underlying pathological processes have been identified such as myocarditis, abnormal autoimmune responses, apoptosis, and impaired cardiac microvasculature.^{4,5} Recent data have shown that unbalanced peripartum/postpartum oxidative stress is linked to proteolytic cleavage of prolactin into a potent antiangiogenic,

proapoptotic, and proinflammatory factor, but the cause of PPCM is still not fully understood.⁶

The position statement from the European Society of Cardiology on the classification of cardiomyopathies classifies PPCM as a nonfamilial, nongenetic form of dilated cardiomyopathy associated with pregnancy.⁷ However, anecdotal cases with familial clustering of PPCM, as well as familial occurrences of PPCM and idiopathic dilated cardiomyopathy (DCM), have been reported, suggesting that genetic factors play a role in the pathogenesis of PPCM.⁸⁻¹⁵ Genetic analysis is not usually performed in PPCM, and so far, no mutations in genes related to hereditary cardiomyopathies have been reported for it.

PPCM probably develops as a result of a complex interaction of pregnancy-associated factors and genetic factors. In other words, against a background of genetic susceptibility, factors associated with pregnancy could lead to PPCM. In this study, we focused on the genetic/familial component of PPCM. We hypothesized that a subset of PPCM cases is part of the spectrum of familial DCM, presenting in the peripar-

Received December 9, 2009; accepted March 13, 2010.

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Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.109.929646

tum period. We followed a 2-tier approach to test this hypothesis: We examined a large Dutch cohort of proven familial DCM cases and reported on the number of PPCM patients found in this cohort, and in the reverse order, we reviewed all the PPCM patients seen in our clinic since the early 1990s and performed cardiological screening of the first-degree relatives of PPCM patients who did not show full recovery. In addition, we analyzed the genes known to be most commonly involved in DCM in these cases. In 1 family, we performed more extensive genetic screening because the index patient was very young at the onset of DCM.

Methods

Clinical Evaluation

PPCM Patients in Families With DCM

Patients with idiopathic DCM or other possible hereditary cardiac disorders are routinely evaluated at the cardiogenetics outpatient clinic of the University Medical Centre Groningen. Our routine procedures include recording the clinical characteristics of the index patient, constructing a pedigree, and inquiring about the family history. Letters are provided for family members at risk to invite them to the outpatient clinic for presymptomatic ("cascade") screening.^{16,17}

DCM is diagnosed when a patient has both a reduced systolic function of the left ventricle (left ventricular ejection fraction <0.45) and dilation of the left ventricle (left ventricular end-diastolic dimension >117% of the predicted value corrected for body surface area and age) and only after identifiable causes like severe hypertension, coronary artery disease, and systemic diseases have been excluded.^{18,19} If only one of these criteria is fulfilled, the case is labeled mild DCM. Familial DCM is diagnosed if there are ≥ 2 affected family members or if a first-degree relative of a DCM patient died suddenly before 35 years of age.¹⁹ We reviewed our database of DCM families, focusing specifically on the presence of PPCM patients in these families and using the diagnostic criteria for PPCM mentioned earlier.¹⁻³ The local institutional review committee approved the study, and all participants gave informed consent.

PPCM Patients and Cardiological Screening of Their Family Members

We reviewed all the PPCM cases collected since the early 1990s by the Department of Cardiology, University Medical Centre Groningen. The available data on the patients' clinical characteristics were carefully evaluated. If a patient had not fully recovered from PPCM within 1 year (normalization of left ventricular function and dimensions), she was invited to the cardiogenetics outpatient clinic to be informed about the possibility of family screening for DCM and DNA analysis. Patients were given family letters to give to their relatives. Those relatives who responded and who, after undergoing genetic counseling, agreed to cardiological screening were subjected to a 12-lead ECG, an echocardiogram, and magnetic resonance imaging (if indicated). The local institutional review committee approved the study, and all the participants gave their informed consent.

Genetic Analysis

Genomic DNA was isolated from blood samples obtained from the index patients of the DCM families with a case of PPCM or from the PPCM patients. DNA samples from 300 ethnically matched control alleles were used as control. DNA analysis was performed for the following DCM-related genes: lamin A/C (*LMNA*), cardiac troponin T (*TNNT2*), and β -myosin heavy chain (*MYH7*). We used genetic techniques (denaturing high-performance liquid chromatography, denaturing gradient gel electrophoresis, and direct sequencing) to screen the protein-coding regions of the exons, as well as the adjacent intronic regions essential for splicing. To detect large deletions or duplications of ≥ 1 exons of *LMNA*, we used the

multiplex ligation-dependent probe amplification test (MRC-Holland, Amsterdam, the Netherlands).²⁰

In family 1b, we performed more extensive DNA analysis because the index patient developed DCM at a very young age (before 2 years of age). In this family, we analyzed almost all the DCM-related genes available in diagnostics (ie, *ACTC1* [cardiac α -actin], *CSRP3* [muscle LIM protein], *DES* [desmin], *LMNA*, *MYBPC3* [myosin-binding protein C], *MYH7*, *TNNT1* [cardiac troponin C], *TNNI3* [cardiac troponin I], *TNNT2*, *TPM1* [α -tropomyosin]). Details of all these analyses are available on request.

Results

PPCM Patients in Families With DCM

Ninety families with idiopathic DCM were available for investigation, and we found 5 families (5 of 90, 6%) with at least 1 case of PPCM. Detailed clinical data of these PPCM patients and their affected family members (families 1a through 1e) are given in Table 1, and their pedigrees are shown in Figure 1. In family 1d, 2 members with PPCM were identified. In family 1b, we identified 1 documented PPCM case and 1 family member who died suddenly just after her second delivery, suggesting that this might also have been a case of PPCM.

PPCM Patients and Cardiological Screening of Their Family Members

We were able to evaluate data from 10 PPCM cases since the early 1990s. Treatment of PPCM patients was performed according to the guidelines for DCM patients. Five patients showed recovery of left ventricular function and dimensions beyond the criteria for DCM within 1 year, and we did not invite them to the cardiogenetics outpatient clinic. One patient was lost to follow-up, and another patient declined our invitation. The remaining 3 patients were seen at the cardiogenetics outpatient clinic. Cardiological screening of their first-degree family members revealed undiagnosed DCM in all 3 families (individuals 2a-II:2, 2b-II:2, and 2c-II:2). Detailed clinical data and the pedigrees of these 3 families are shown in Table 2 and Figure 2.

Genetic Analysis

We analyzed the DNA of the index patients of the 5 DCM families with at least 1 case of PPCM and of the 3 PPCM patients but found no mutations in *LMNA*, *TNNT2*, and *MYH7*. However, in family 1b, in which we performed more extensive DNA analysis, we identified a mutation in cardiac troponin C (c.149A>G, p.Gln50Arg in *TNNT1*; see Figure 3A). This mutation was seen in the index patient, in her affected mother (III:1), and in one of her 2 affected maternal great-aunts (II:4), implying that the grandmother (II:1) was an obligate carrier of this mutation. Individual II:5, an affected maternal great-aunt, refused DNA analysis. This mutation is believed to be pathogenic because (1) it alters a glutamine residue, which is highly conserved all the way up to the nematode *Caenorhabditis elegans* and is surrounded by conserved residues (see Figure 3B); (2) the amino acid substitution is localized in a small critical linker region (3 amino acids) between 2 calcium-binding/EF-hand (helix-loop-helix) domains known to be involved in protein-protein

Table 1. Clinical Features of Affected Members of DCM Families With PPCM Patients

Patient	Referred for	Diagnosis	Age at Diagnosis	Timing at Diagnosis	LVEF at Diagnosis, %	Pathology	Cardiological Remarks	Other Remarks	Follow-Up
1a-I:2	HF	DCM	51 y						
1a-II:1*	HF	PPCM	33 y	35th wk of pregnancy	23		Thrombus apex, sinus tachycardia	CS	LVEF 44% after 6 mo, stable for 4 y
1b-II:1	Died	DCM	54 y			Dilated heart, enlarged and hyperchromatic nuclei of the myocytes			
1b-II:2*	Died	SCD	26 y	Just after delivery		NA			
1b-II:4	Screening	Mild DCM	63 y						
1b-II:5	Screening	Mild DCM	62 y						
1b-III:1*	HF	PPCM	30 y	3 mo after delivery	21				No recovery after 9 mo
1b-IV:1	Heart murmur	DCM	16 mo						
1c-I:1	Died	DCM	63 y			NA			
1c-II:2	HF	DCM	41 y				LBBB		
1c-II:3*	HF	PPCM	26 y	Few days after delivery	NA	Dilated heart, myocyte hypertrophy, fibrosis	LBBB		Died after 2 wk of intractable HF
1c-III:1	Screening	Mild DCM	25 y						
1c-III:3	Screening	DCM	22 y						
1c-III:4	Screening	DCM	20 y						
1c-III:5	Screening	DCM	28 y						
1 d-II:1	Dyspnea	DCM	61 y						
1 d-II:3	Screening	DCM	61 y						
1 d-II:5*	HF	PPCM	29 y	Just after delivery	NA	NA			Died at 31 y of age
1 d-III:2*	Cardiogenic shock	PPCM	27 y	3 d after delivery	20	Mild hypertrophy of myocytes			Died within 1 mo of MOF
1 d-III:3	Screening	DCM	48 y						
1 d-III:4	Screening	DCM	48 y						
1e-II:1	AF	DCM	74 y				AF		
1e-II:3	Dyspnea	DCM	70 y				AF		
1e-III:2*	HF	PPCM	29 y	2 mo after delivery	23	EMB: signs of acute myocarditis, no autopsy	Developed AF	Suspicion of vasculitis, no primary APS	No recovery, died at 51 y of age of progressive HF

LVEF indicates left ventricular ejection fraction; HF, heart failure; CS, caesarean section; SCD, sudden cardiac death; LBBB, left bundle-branch block; MOF, multiorgan failure; AF, atrial fibrillation; EMB, endomyocardial biopsy; NA, not available; and APS, antiphospholipid syndrome.

*Presumed PPCM cases.

interactions (the p.Gln50Arg mutation probably perturbs normal function of this important domain); (3) the mutation cosegregates with disease in this family; (4) the mutation was absent in 300 alleles from ethnically matched control individuals; and (5) the mutation is classified as pathogenic by several prediction algorithms (Polyphen prediction: “probably damaging” [high confidence of affecting protein function or structure]; SIFT prediction: not tolerated [score, 0.00; SIFT scores range from 0 to 1, with 0 indicating the most deleterious mutation and 1 indicating the least deleterious mutation]). Moreover, *TNNC1* is very highly conserved, and only a few sequence variants are found in this gene, which underpins our conclusion that the mutation in this family is pathogenic.

Discussion

This is the first study reporting a systematic approach to investigating the relation between PPCM and familial DCM. We identified a substantial number (5 of 90, 6%) of DCM families

with PPCM patients. This number is considerably higher than would be expected by chance. Although the incidence of PPCM in the Netherlands is unknown, it has been reported that the incidence in the United States is only 1 in 4075 live births.²¹ Second, in our exploratory study, undiagnosed DCM was identified in all 3 families of PPCM patients who did not show full recovery. Finally, the identification of a mutation (c.149A>G, p.Gln50Arg) in *TNNC1* in a DCM family with 1 PPCM patient and another family member who had died suddenly soon after a delivery underscores the genetic nature of this disease. Together, these findings strongly suggest that a subset of PPCM is part of the spectrum of familial DCM, presenting in the peripartum period. Hence, the statement from the European Society of Cardiology on the classification of cardiomyopathies, which classifies PPCM as a nonfamilial, nongenetic form of dilated cardiomyopathy associated with pregnancy,⁷ may need to be reconsidered if more extensive multicenter studies confirm our findings.

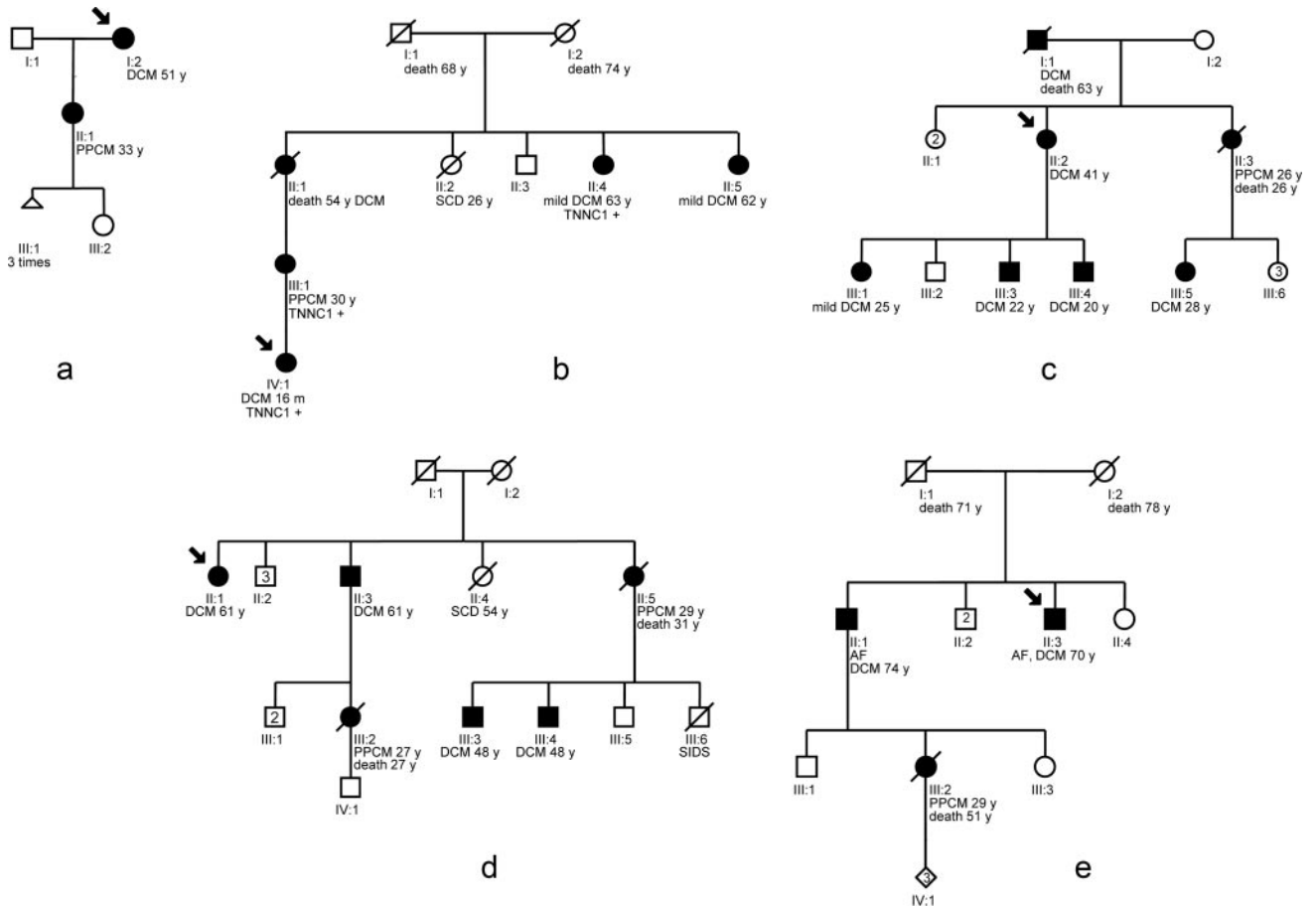


Figure 1. Pedigrees of DCM families with PPCM patients. Square symbols indicate men; circles, women; diamonds, unknown sex; and triangles, miscarriage. Solid symbols indicate clinical diagnosis of PPCM or (mild) DCM. Diagonal lines through symbols indicate deceased; arrow indicates index patient in each family; and the number in a symbol indicates the number of individuals with this symbol. AF indicates atrial fibrillation; SCD, sudden cardiac death; SIDS, sudden infant death syndrome; and TNNC1+, carrier of mutation p.Gln50Arg in *TNNC1* (cardiac troponin C).

Pathophysiology of PPCM and Role of Genetic Predisposition

Since its first description in 1849,^{22,23} PPCM has remained an intriguing disease entity that often poses a significant challenge to the clinician. The diagnosis of PPCM is often delayed; an important reason for this delay is probably related to the fact that

the cardinal symptoms of PPCM (fatigue, dyspnea, edema) are also associated with a normal pregnancy.²⁴ In addition, although the clinical course is often benign with recovery of left ventricular function and dimensions, a considerable subset of patients with PPCM progress to intractable heart failure necessitating heart transplantation.²⁵

Table 2. Clinical Features of PPCM Patients and Their Affected Family Members Identified by Cardiological Screening

Patient	Referred for	Diagnosis	Age at Diagnosis, y	Timing at Diagnosis	LVEF at Diagnosis, %	Cardiological Remarks	Other Remarks	Follow-Up
2a-II:2	Screening, fatigue, palpitations	DCM	57					
2a-III:1*	HF	PPCM	33	37th wk of pregnancy	25		CS	LVEF 35% after 3 mo
2b-II:2	Screening	DCM	61					
2b-III:1*	HF	PPCM	23	Just after delivery	25		CS in 28th wk because of eclampsia	LVEF 10% after 8 y, CRT
2c-II:1*	TIA, PE	PPCM	33	2 mo after delivery	20	Thrombus in both ventricles	TIA, PE	LVEF 45% after 8 y
2c-II:2	Screening	Mild DCM	58					

LVEF indicates left ventricular ejection fraction; HF, heart failure; CS, caesarean section; CRT, cardiac resynchronization therapy; TIA, transient ischemic attack; and PE, pulmonary embolism.

*PPCM cases.

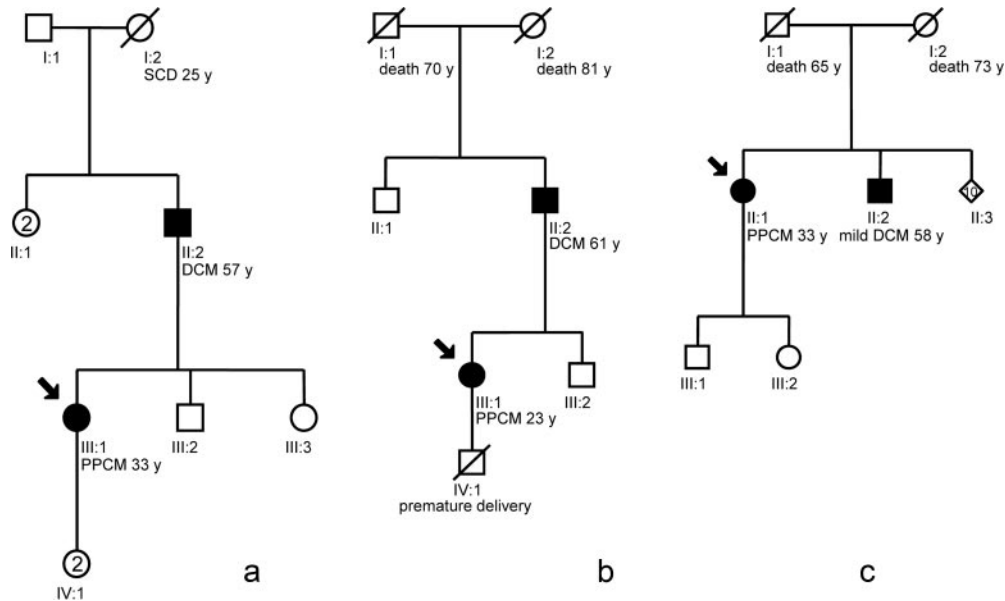


Figure 2. Pedigrees of the families of PPCM patients in which cardiological screening revealed undiagnosed cases of DCM. Square symbols indicate men; circles, women; and diamonds, unknown sex. Solid symbols indicate clinical diagnosis of PPCM or (mild) DCM. Diagonal lines through symbols indicate deceased; arrows indicate index patient in each family; and the number in a symbol indicates the number of individuals with this symbol. SCD indicates sudden cardiac death.

The cause of PPCM is still unresolved, but a unifying concept was recently proposed that explains several key features of PPCM. Oxidative stress rises during normal pregnancy, culminating in the last trimester; this runs parallel to an increase in antioxidant capacity with a peak early after delivery.²⁶ Several signaling pathways have been shown to be required for protection of the maternal heart, including c-Src-Akt and STAT3. In a mouse model, a deletion of *STAT3* caused proteolytic cleavage of prolactin into a potent antiangiogenic, proapoptotic, and proinflammatory factor associated with the development of PPCM.⁷ The attractiveness of this concept notwithstanding, it does not explain why only a few women develop PPCM while the majority remain unaffected. As suggested by previous case reports, genetics may play a role: 4 reports describe a total of 8 kinships with >1 member with PPCM.^{8–13} Moreover, 2 families have been reported with cases of PPCM and DCM in close relatives.^{14,15}

In this study, we took a systematic approach to investigate the role of genetics in PPCM. We hypothesized that a subset of PPCM cases might occur against a background of familial DCM and found supporting evidence for this hypothesis. We identified PPCM cases in 5 of 90 families (6%) with DCM,

and we found undiagnosed DCM in all 3 families of PPCM patients who did not show full recovery. It is also worth noting that 2 families (1b and 1d) probably had >1 member with PPCM.

In terms of pathophysiology, the following scenario has begun to emerge: There may be an interaction between environment and genetics in the sense that peripartum/postpartum oxidative stress (“environment”) causes a genetically susceptible woman (“genetics”) to cross the threshold toward overt DCM. More precisely, in women with a familial predisposition for DCM, the oxidative stress associated with the peripartum/postpartum period may trigger the manifestation of disease. However, it should be noted that familial predisposition can explain only part of the problem because even in DCM families only a minority of women develop PPCM.

Relative to the time window of PPCM, Elkayam and coworkers²⁷ reported that the clinical presentation and outcome of women with pregnancy-associated cardiomyopathy that was diagnosed early in pregnancy are comparable to those of women with formal PPCM. In fact, we also observed several cases of overt DCM before the last month of pregnancy in women from DCM families who had no prior

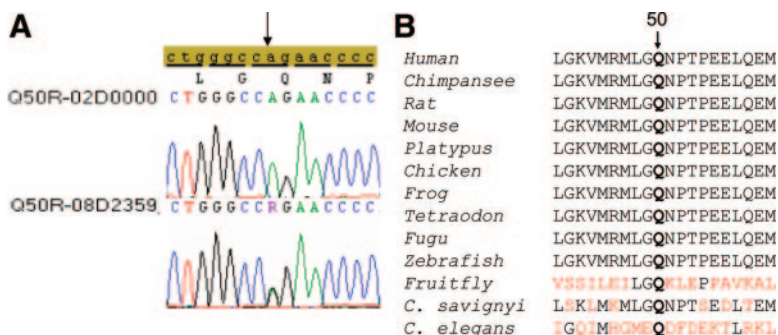


Figure 3. *TNNC1* mutation p.Gln50Arg. A, Sequence trace showing the presence of the p.Gln50Arg mutation in the index patient. Sequence trace of the relevant *TNNC1* fragment from a control DNA sample (02D0000) and from a sample of the index patient (08D2359) showing the A to G nucleotide change at position 149 (c.149A>G) leading to the missense mutation p.Gln50Arg. Mutation nomenclature according to www.HGVS.org. Arrow indicates nucleotide position 149. B, Sequence alignment showing cross-species conservation of the glutamine residue (Q) at position 50 of *TNNC1* up to the nematode *C. elegans*.

history of heart disease (data not shown). In these instances, however, there is an alternative explanation, namely the hemodynamic challenge associated with pregnancy triggering overt DCM in the setting of subclinical DCM. To avoid any confusion, we adhered to the strict definition of PPCM, including the limited time window.

Genetic Analysis

We analyzed the genes believed to be most commonly involved in DCM (*LMNA*, *TNNT2*, and *MYH7*) but found no mutations. This is not surprising because the yield of DNA analysis in patients with DCM is, in general, still rather low (<20%), even when analyzing a relatively large batch of genes.²⁸ However, after extensive DNA analysis in family 1b, we did identify a mutation in *TNNC1* (p.Gln50Arg), supporting the genetic nature of the disease in this DCM family with a PPCM case. Moreover, this finding is important for the genetics of DCM in general because, to the best of our knowledge, only 1 germline *TNNC1* mutation (p.Gly159Asp) related to DCM has been reported in the literature so far.^{29,30}

Disease expression in the family with the *TNNC1* mutation (p.Gln50Arg) is extremely variable (see Table 1). The index patient was diagnosed with DCM before 2 years of age; the mother developed PPCM after her first pregnancy; the maternal grandmother had no problems during her pregnancy, although she was diagnosed with DCM postmortem at 54 years of age; one of the grandmother's sisters died suddenly at 26 years of age just after her second delivery; and 2 other sisters of the grandmother were diagnosed with only mild DCM after screening but neither had problems during their pregnancies (3 and 2, respectively). In the previously reported DCM family with a *TNNC1* mutation (p.Gly159Asp), expression of the disease was severe, with several family members experiencing premature cardiac death or transplantation.²⁹ Remarkably, this family also had 1 member who had been diagnosed with DCM in childhood, whereas development of DCM in childhood is usually very rare in DCM families.³⁰ Further studies on the presence and effects of *TNNC1* mutations in PPCM patients and DCM families, including DCM diagnosed in childhood, are required to clarify the relationship between these conditions, the disease expression, and this gene.

Limitations

One important limitation of this study is that we did not perform cardiological screening of family members of those PPCM patients who had recovered left ventricular function and dimensions beyond the criteria for DCM. At the time we designed this study, we believed that we could not clinically or ethically justify offering presymptomatic cardiological screening to these families because the chances of identifying clinically relevant findings seemed smaller than the possible side effects (like psychological stress, unforeseen diagnostic findings outside this context, and problems with health insurance) that might arise from such screening. However, given our results, it would be interesting to study these families because these PPCM cases might also be part of familial DCM.

Another limitation is the small number of PPCM cases in this study. The finding of undiagnosed DCM in all 3 analyzed families of PPCM patients may be overrepresented, and larger numbers are necessary to assess the real incidence of this phenomenon. Therefore, a more extensive multicenter, systematic cardiological screening study of first-degree relatives of PPCM patients, including the relatives of recovered PPCM patients, is important. This would provide the opportunity to confirm our results and to study the relation of PPCM and familial DCM in more detail.

It is notable that the outcome of the 6 PPCM cases in the DCM families appears to be worse (see Table 1) than the known characteristics of PPCM in general, in which a subset has a benign course with recovery of left ventricular function and dimensions. Larger numbers of cases are needed to allow a comparison of the clinical characteristics of PPCM cases in DCM families with isolated PPCM cases.

Conclusions and Practical Implications

To the best of our knowledge, this is the first systematic study of the relation between PPCM and familial DCM. We found cases of PPCM in 5 of 90 DCM families and identified previously undiagnosed DCM in the families of all 3 PPCM patients who did not show a full recovery. We found support for the genetic nature of disease in 1 DCM family with PPCM by identifying a mutation in *TNNC1*. We therefore conclude that PPCM can be a manifestation of familial DCM.

Obviously, further research is needed to confirm our findings, for instance, to better understand the interaction between oxidative stress associated with the peripartum/postpartum period and genetics. However, our findings already have several practical implications. First, because PPCM can be the first manifestation of familial DCM, we recommend presymptomatic screening for covert DCM in first-degree family members of PPCM patients without recovery of left ventricular function and dimensions. Second, as part of routine procedures, we already follow healthy women (ie, without proven previous signs of DCM) during pregnancy if they are first-degree family members of affected individuals in a DCM family, but this monitoring should be extended to the puerperium.

Acknowledgments

We thank all the patients who participated in this study; Karin Berkenbosch, genetic counselor, for counseling some of the families; Ronald Lekanne dit Deprez, PhD, clinical molecular geneticist, for the *TNNT2* analysis; and Jackie Senior for editing this manuscript.

Disclosures

None.

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CLINICAL PERSPECTIVE

Anecdotal cases with familial clustering of peripartum cardiomyopathy (PPCM) or joint occurrence of PPCM and idiopathic dilated cardiomyopathy (DCM) within families have been reported. We performed the first systematic study of the relation between PPCM and familial DCM. In a substantial number of DCM families (5/90), cases of PPCM were found, and more important, previously undiagnosed cases of DCM were identified in all 3 families of PPCM patients who did not show a full recovery. Moreover, our results support the genetic nature of the disease in 1 DCM family with PPCM: We identified a mutation in the gene encoding cardiac troponin C (*TNNC1*). We therefore conclude that PPCM can be a manifestation of familial DCM. Obviously, further research is needed to confirm these observations in a larger series of patients. However, our findings already have several clinical implications and may change clinical practice and thinking about PPCM. Because PPCM can be the first manifestation of familial DCM, we recommend presymptomatic cardiological screening for covert DCM in first-degree family members of PPCM patients without recovery of left ventricular function and dimensions. Second, cardiological screening during pregnancy should be considered for healthy women (ie, without proven previous signs of DCM) who are first-degree family members of familial DCM patients and this should be extended into the puerperium.