

Received: 2018.02.23  
Accepted: 2018.04.23  
Published: 2018.07.12

e-ISSN 1941-5923  
© Am J Case Rep, 2018; 19: 820-824  
DOI: 10.12659/AJCR.909601

## Severe Course of Peripartum Cardiomyopathy and Subsequent Recovery in a Patient with a Novel TTN Gene-Truncating Mutation

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
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**Conflict of interest:** None declared

**Source of support:** This study was funded by grant 2.56/II/2014 GT from the Institute of Cardiology (<http://www.ikard.pl/home.html>) and by grants 2013/11/N/NZ2/02528 MF and 2011/01/B/NZ4/03455 RP from the National Science Centre Poland (<https://www.ncn.gov.pl/>). ZTB's work is supported by the DETECTIN-HF project (ERA-CVD framework)

**Patient:** Female, 25  
**Final Diagnosis:** Peripartum cardiomyopathy  
**Symptoms:** Fatigue • orthopnoea • pulmonary edema • tachycardia  
**Medication:** —  
**Clinical Procedure:** —  
**Specialty:** Cardiology

**Objective:** Unknown etiology

**Background:** Peripartum cardiomyopathy (PPCM) is a potentially life-threatening, pregnancy-associated cause of heart failure affecting previously healthy women. Recent research suggests a possible role of 16-kDa prolactin in promoting cardiomyocyte damage. However, the genetic predisposition is not well recognized.





**Case Report:** We report the case of a 25-year-old woman with a severe course of PPCM with left ventricle ejection fraction of 25–30%, complicated by ventricular arrhythmia and postpartum thyroiditis. As no traditional risk factors of PPCM were identified, the patient was referred for genetic testing. Next-generation sequencing revealed a novel titin gene-truncating mutation NM\_001267550: p.Leu23499fs/c.70497\_40498insT in the proband as well as in her mother.

In the patient, a very late recovery >12 months postpartum was observed, which required long-term medical treatment with bromocriptine.

**Conclusions:** PPCM may occur in women with the genetic predisposition, being modified by an interaction of biological factors, such as a high prolactin level, a ventricular arrhythmia, and an autoimmune disorder. Recovery from severe heart failure due to an inherited cardiomyopathy is possible with careful and appropriate medical management.

**MeSH Keywords:** **Cardiomyopathy, Dilated • Frameshift Mutation • Heart Failure • Pregnancy Complications, Cardiovascular**

**Full-text PDF:** <https://www.amjcaserep.com/abstract/index/idArt/909601>

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## Background

Peripartum cardiomyopathy (PPCM) is a multi-etiological disease in women without previously known heart disease, occurring during the final months of pregnancy or in the first months after delivery [1]. Patients present with left ventricle (LV) heart failure (HF) and reduced LV ejection fraction (EF) <45%. In women with a family history of dilated cardiomyopathy (DCM), mutations in the titin (TTN) gene were most frequent and the reported recovery rate was very low [2]. We present the case of a woman with PPCM and a novel TTN gene-truncating mutation.

## Case Report

A 25-year-old nulliparous white woman, 36 weeks pregnant, was admitted to hospital with new onset of severe HF. Shortly before pregnancy, the patient had suffered from orthostatic fainting and had had an echocardiogram performed, which revealed no abnormalities, including normal left ventricle size with LVEF of 60%.

At admission, echocardiography revealed dilated, hypokinetic LV with an ejection fraction (EF) of 25–30% and significant mitral insufficiency. A cesarean section under general anesthesia was performed in a cardiac surgery operating theatre, and a healthy male infant was delivered. Afterwards, standard HF pharmacotherapy and bromocriptine were introduced. Cardiovascular magnetic resonance confirmed nonischemic cardiomyopathy with severe impairment of the left and right ventricle (RV) function with a RVEF of 22% (Figure 1A, 1B). In the eighth week of treatment, the patient's condition improved. The patient was discharged in the tenth week with an LVEF of 32%. However, in the fourth month, the patient presented with postpartum thyroiditis. Due to an increasing number of VT episodes, the patient required radio-frequency ablation treatment. The bromocriptine was continued for almost 12 months due to an increasing level of serum prolactin (503 mIU/l) after a temporary discontinuation of treatment (Figure 1C). At 12-month follow-up, LVEF improved up to 54%, but the LV longitudinal systolic function remained at a depressed level and significant mitral insufficiency persisted (Figure 1D, 1E).

The patient was referred for clinical genetic testing. Next-generation sequencing (NGS) in the proband was performed using the TrueSight One (TSO, Illumina, San Diego, California, United States) sequencing panel. A novel frameshift insertion NM\_001267550: p.Leu23499fs/c.70497\_40498insT of TTN gene was identified in the proband and in the proband's asymptomatic 50-year-old mother but not in her younger sister (Figure 2). The patient's father had died at the age of 40 in an accident.

## Discussion

This case shows that PPCM is a complex, multifaceted phenomenon. PPCM is associated with a high mortality rate, which varies from 1.36% (in-hospital mortality) to 30% (over a 47-month observation) [1].

Traditional risk factors for PPCM include: multiparity, pre-eclampsia, advanced or early maternal age (>30 or <18 years), prolonged use of  $\beta$ -agonists, family history, ethnicity, smoking, diabetes, hypertension, and previous incidence of PPCM [1].

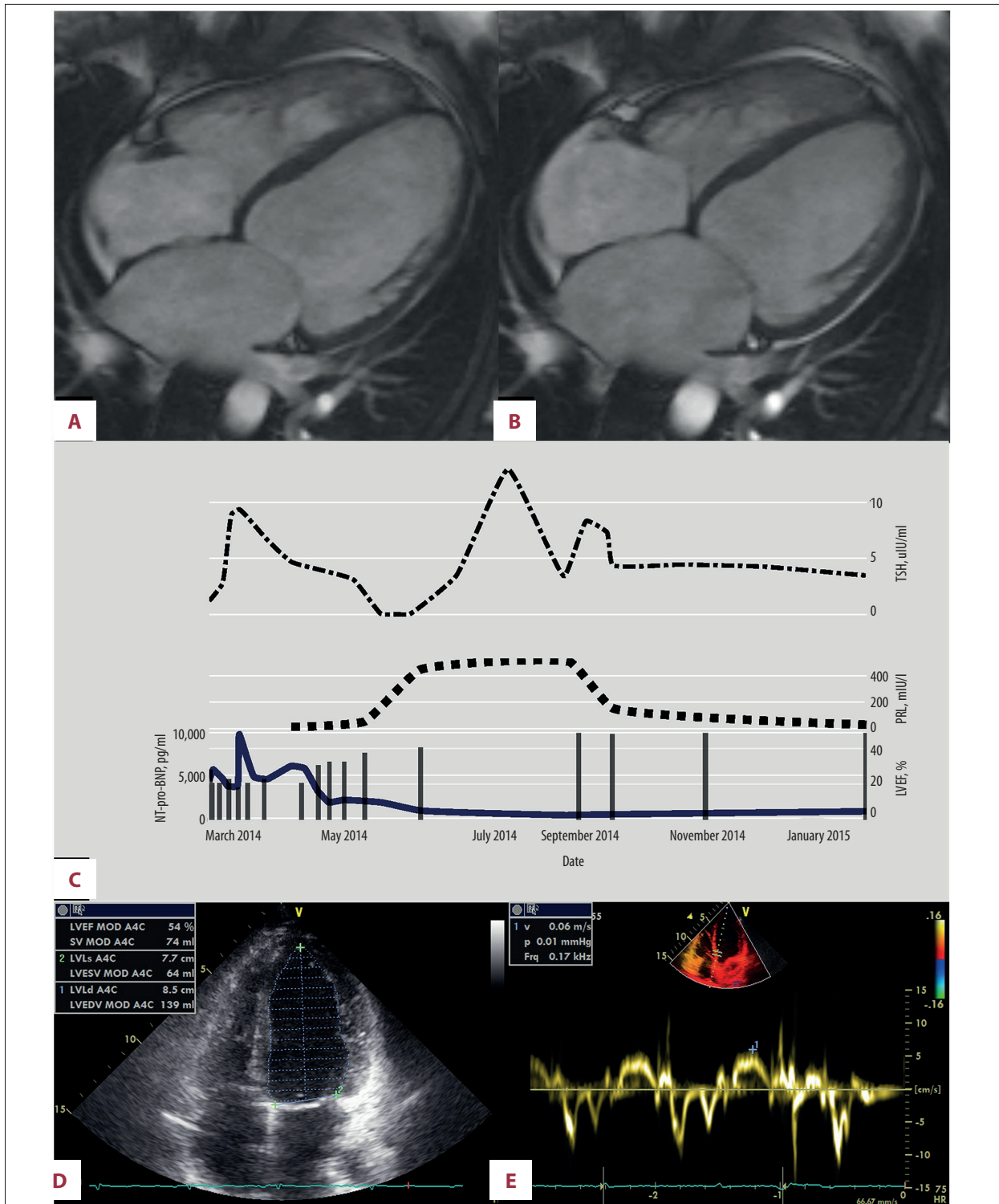
Mutations in the TTN gene have been reported as pathogenic in women with PPCM and a family history of DCM [2]. However, as far as we are aware, the frameshift mutation identified in our patients has not been described before [3]. Mutations in the TTN gene lead to the functional change of titin and decreased passive force compared to controls [2].

In this case, the proband's mother is an obligate carrier. However, the proband's father's premature death and lack of contact with the patient's distant relatives precluded a full assessment of a family history of DCM. The patient had no traditional risk factors, which indicates that the identified TTN truncating variant was a major contributing factor to the development of PPCM.

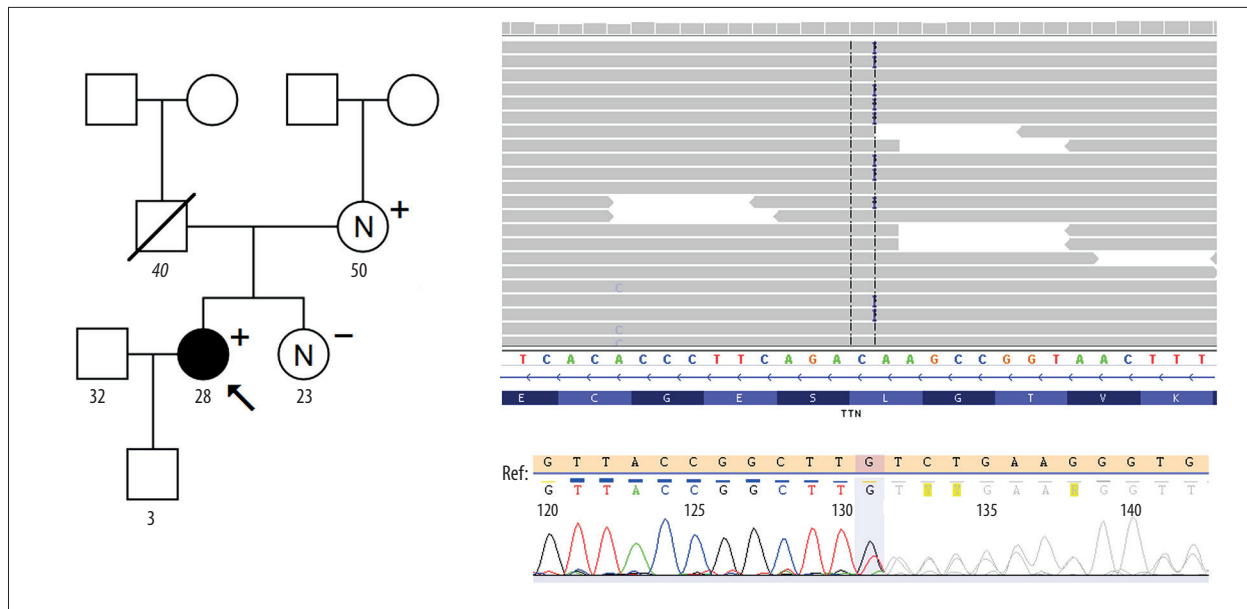
The rate of recovery from PPCM is particularly low in the case of LVEF <30% and LVEDd >60 mm [4]. The period of 3–6 months should be considered as a minimum time to recovery, yet cases of very late (>12 months up to 5 years) recoveries have been reported [5].

The condition of our patient with severe LV insufficiency improved during optimal standard HF therapy combined with bromocriptine. However, her LVEF only exceeded 50% at 12 months after delivery.

This result is contrary to the reported very low recovery rate of PPCM cases with a family history of DCM and underlying mutations [2]. However, in our patient's family, only her mother has the TTN truncating variant identified, with no established penetrance so far. This case is consistent with recent results indicating no differences in recovery rate or major cardiac event rate between DCM patients with and without TTN truncation [6]. Moreover, the incomplete disease penetrance (62–82%) was more pronounced in women compared to men [7]. This pattern suggests that while TTN mutations predispose to cardiomyopathy, there are other additional biological, genetic, or environmental risk factors that may influence the course of the disease, especially in women [7].



**Figure 1. Top:** Severe impairment of the systolic function of the left and right ventricles by cardiac magnetic resonance in the first week after delivery (**top**); 4-chamber view: (**A**) diastolic (**B**) systolic; middle: (**C**) The relation of left ventricle (LV) ejection fraction (EF) (bars) to levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP; reference:  $\leq 125$  pg/ml), prolactin (PRL; reference range: 102–496 mIU/l) and thyroid-stimulating hormone (TSH; reference range: 0.27–4.2  $\mu$ IU/ml); **bottom:** Echocardiography at 12-month follow-up: (**D**) improved LVEF; (**E**) decreased LV longitudinal systolic function by tissue Doppler.



**Figure 2.** The titin (TTN) gene mutation in the proband; **left:** Pedigree of the family, **right hand side top:** Next-generation sequencing (NGS) result using Integrative Genomics Viewer (IGV) screen shot; **right hand side bottom:** Corresponding chromatogram from Sanger sequencing.

In our case, one of these factors may be a high prolactin level. Bromocriptine, which decreases the synthesis of prolactin and consequently its 16-kDa fragment of proven cardiotoxic and vascular impairing effects, was reported to have a beneficial effect in PPCM treatment [8]. Although longer-term treatment with bromocriptine appears to have been effective in the case of our patient, the efficacy of such treatment in general remains to be proven.

A ventricular arrhythmia may be a second factor causing heart muscle damage and consequent penetrance of TTN mutations. Patients with an LVEF <30% are at the highest risk of life-threatening arrhythmias, but LV impairment in PPCM may be reversible [2].

Our patient had severe heart failure for 7 weeks, and she might have been considered as a candidate for ICD implantation. However, according to guidelines, the decision about the implantation of ICD should be made after 4–6 months of optimal medical therapy [9]. If available, a wearable cardiac defibrillator (WCD), a device capable of analyzing the electric activity of the heart and generating an electric impulse when necessary, should be considered in PPCM patients with LVEF under 35% for 6 months [10].

Postpartum thyroiditis, which is an autoimmune disorder, may be another factor influencing cardiac function [11]. Moreover, the autoimmune reaction could have acted as an additional pathophysiological factor of PPCM in the case of this patient [1]. Additionally, our case shows that the number of the additional pathophysiological factors may be important for the penetrance of the TTN mutation, as our patient's mother has stayed asymptomatic to date.

## Conclusions

Truncating mutations of the TTN gene may be pathogenic in PPCM cases, especially in patients with no traditional risk factors of PPCM. Despite the genetic burden, recovery from this cardiomyopathy is possible. Multidisciplinary care is crucial for satisfactory outcome of patients with severe PPCM; prolonged treatment with bromocriptine, guided by serum prolactin levels, is particularly beneficial. Strict ambulatory monitoring is very important due to the risk of developing other cardiac and extracardiac conditions.

## Conflict of interest

None.

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