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RESEARCH LETTER

Overall Survival Rate of Patients With Triglyceride Deposit Cardiomyovasculopathy

Triglyceride deposit cardiomyovasculopathy (TGCV) is an emerging, rare cardiovascular disorder (Orphanet ORPHA code: 565612) first reported in 2008 in patients requiring cardiac transplantation.[1] TGCV is caused by defective intracellular lipolysis of triglyceride (TG) leading to heart failure and diffuse narrowing atherosclerosis with TG deposition. Since 2009, the Japan TGCV study group has elucidated its pathophysiology and developed diagnostic methods and specific treatments as a part of a governmental rare disease project.

It is difficult to diagnose TGCV because plasma TG level or body mass index is not relevant. Moreover, postmortem pathological screening indicated that a substantial number of patients with TGCV had died without any clinical diagnosis. The only known genetic cause for TGCV is homozygous mutations in *PNPLA2*, encoding adipose TG lipase, an essential enzyme for the intracellular hydrolysis of TG.[1] However, in the majority of patients identified with TGCV, genetic adipose TG lipase mutations were not present; thus, underlying genetic etiology remains unknown. Based on the Japan TGCV study group diagnostic criteria, a definite diagnosis requires at least one of the following factors related to defective intracellular lipolysis: 1) reduced washout rate (<10%) of iodine-123-β-methyl-p-iodophenylpentadecanoic acid assessed by myocardial scintigraphy; 2) presence of lipid droplets in cardiomyocytes; or 3) myocardial TG accumulation demonstrated by magnetic resonance spectroscopy/computed tomography scan. The most important indicators of clinical severity are reduced left ventricular ejection fraction (<40%), diffuse narrowing coronary atherosclerosis, and typical Jordans' anomaly in peripheral leukocytes.[2]

Prior to 2015, only 25 patients had been clinically diagnosed with TGCV. Subsequently, 2 regional cohort studies were established owing to increasing TGCV awareness,[3-5] and the association of TGCV with high rates of restenosis after percutaneous coronary intervention, even when using second-generation drug-eluting stents.[3] TGCV is more common among patients with diabetes mellitus,[3] hemodialysis,[4] or chronic heart failure with unknown etiologies.[5] Patients with TGCV have higher rates of adverse cardiovascular events when compared to non-TGCV controls.[4,5] The TGCV registry is supported by the Japan Agency of Medical Research and Development (NCT05345223).

The objective of this study was to examine survival in patients with TGCV from the TGCV registry. All adult patients diagnosed with TGCV before December 2021 were included. Patients who received dietary therapy with tricaprin were excluded from the analysis because tricaprin, a class of medium-chain TG, was recently proven to facilitate myocardial lipolysis in an investigator-initiated randomized controlled trial setting in patients with TGCV.[6] Data were collected from the university hospitals where the TGCV had been diagnosed. The data collected included birth date, age at diagnosis, sex, adverse nonfatal cardiovascular events, and date and cause of death, if applicable. Nonfatal cardiovascular events included revascularization, stroke, hospitalization of heart failure, and hospitalization, device implantation, or appropriate operation for arrhythmias. Overall and cardiovascular event-free survival rates were estimated using the Kaplan-Meier method with Greenwood confidence intervals. The number of deaths and nonfatal cardiovascular events in 5 years are described in **Table 1**. The data were managed at the Data Center of the Osaka University Hospital. The study was approved by the ethical review boards of participating institutions (Approval No. 20334).

In total, 183 study patients (76% male) were included in the study with a mean age of 64.8 years (range: 24-93 years). The mean age of male and female patients at TGCV diagnosis was 63.6 (range: 24-87 years) and 68.6 years (range: 33-93 years), respectively. The prevalence of coronary artery disease, heart failure, and ventricular arrhythmia was 74.9%, 71.0%, and 26.2%, respectively. The mean follow-up time was 2.9 years. Five years after diagnosis, 39 patients had died (31 male and 8 female), with the mean age being 71.0 years (range:

TABLE 1 Clinical Profiles, Survival Rates, and Cardiovascular Events in Patients With Triglyceride Deposit Cardiomyovasculopathy

		Total (N = 183)		Male (N = 139)		Female (N = 44)	
Clinical profiles							
Age of diagnosis (y)							
Mean ± SD		64.8 ± 14.1		63.6 ± 13.7		68.6 ± 14.6	
Median (IQR)		66.0 (57.0-76.0)		65.0 (56.0-74.0)		71.0 (59.0-80.5)	
Range		24-93		24-87		33-93	
Cardiac phenotypes							
Coronary artery disease		137 (74.9)		104 (74.8)		33 (75.0)	
Heart failure		130 (71.0)		101 (72.7)		29 (65.9)	
Ventricular arrhythmia		48 (26.2)		40 (28.8)		8 (18.2)	
Survival rates[a]	Period	At risk		At risk		At risk	
Overall survival	3 y	88	80.1 (72.8-85.5)	66	78.7 (70.1-85.1)	22	84.4 (68.4-92.8)
	5 y	19	71.8 (62.6-79.0)	15	70.9 (60.3-79.1)	4	74.2 (52.6-87.1)
Cardiovascular event[b]-free survival	3 y	62	60.9 (52.4-68.4)	45	58.7 (48.8-67.3)	17	67.9 (49.7-80.7)
	5 y	13	54.0 (44.5-62.7)	9	49.6 (38.4-59.8)	4	67.9 (49.7-80.7)
Number of events							
All deaths		39 (21.3)		31 (22.3)		8 (18.2)	
Cardiovascular death		27		22		5	
Noncardiovascular death		4		4		0	
Undetermined		8		5		3	
Nonfatal cardiovascular events[c]		55 (30.1)		45 (32.4)		10 (22.7)	
Revascularization (CABG or PCI)[d]		21		18		3	
Stroke[d]		6		5		1	
Hospitalization of heart failure[d]		32		25		7	
Hospitalization or device operation of arrhythmia[d]		5		5		0	

[a]() indicates 95% confidence interval based on Greenwood's method. [b]Cardiovascular events included cardiovascular death and nonfatal cardiovascular events described in the table above. [c]Number (%) of patients who had at least 1 of the following events. [d]Base numbers of patients with indicated nonfatal cardiovascular events.
CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

42-93 years). The mean age at death was slightly lower in male patients (70.4 years, range: 42-89 years) than in female patients (73.6 years, range: 45-93 years). The 3-year overall survival rate was 80.1% (78.7% for males and 84.4% for females) and the 5-year overall survival rate was 71.8% (70.9% for males and 74.2% for females). The causes of the 39 deaths were cardiovascular in 27 patients, non-cardiovascular in 4, and undetermined in 8. The 3-year and 5-year cardiovascular event-free survival rates were 60.9% and 54.0%, respectively. The following nonfatal cardiovascular events were reported: revascularization (n = 21), stroke (n = 6), hospitalization for heart failure (n = 32), and hospitalization or device implantation or appropriate operation for arrhythmias (n = 5).

The present study is the first to report on survival in patients with TGCV. Patients were typically diagnosed in their mid-60s and by 5 years, half had had an adverse cardiovascular event and almost 30% had died. It is encouraging that a clinical trial for the first orphan drug for TGCV, CNT-01, containing purified tricaprin/trisdecanoin, is underway (jRCT2051210177). A limitation of the study is the relatively small cohort size, making it difficult to confirm sex-specific differences in prevalence. Further advocacy, awareness, and recognition by cardiologists and other health care professionals, patients, and the public is paramount in order to improve TGCV detection and treatment.

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REFERENCES

1. Hirano K, Ikeda Y, Zaima N, Sakata Y, Matsumiya G. Triglyceride deposit cardiomyovasculopathy. *N Engl J Med*. 2008;359:2396–2398. https://doi.org/10.1056/NEJMc0805305

2. Kobayashi K, Sakata Y, Miyauchi H, et al. The diagnostic criteria 2020 for triglyceride deposit cardiomyovasculopathy. *Ann Nucl Cardiol*. 2020;6:99–104. https://doi.org/10.17996/anc.20-00131

3. Nakano Y, Suzuki M, Hirano K, et al. Association of triglyceride deposit cardiomyovasculopathy with drug-eluting stent restenosis among patients with diabetes. *JAMA Netw Open*. 2020;3:e2012583. https://doi.org/10.1001/jamanetworkopen.2020.12583

4. Onishi T, Nakano Y, Hirano K, et al. Prevalence and clinical outcomes of triglyceride deposit cardiomyovasculopathy among hemodialysis patients. *Heart*. 2021;107:127–134. https://doi.org/10.1136/heartjnl-2020-317672

5. Aoshima C, Fujimoto S, Kudo A, et al. Clinical significance of 123I-BMIPP washout rate in patients with uncertain chronic heart failure. *Eur J Nucl Med Mol Imaging*. 2022;49:3129–3139. https://doi.org/10.1007/s00259-022-05749-1

6. Miyauchi H, Hirano K, Nakano Y, et al. 123I-BMIPP scintigraphy shows that CNT-01 (tricaprin) improves myocardial lipolysis in patients with idiopathic triglyceride deposit cardiomyovasculopathy: first randomized controlled, exploratory trial for TGCV. *Ann Nucl Cardiol*. 2022;8:67–75. https://doi.org/10.17996/anc.22-00167