

# Triglyceride deposit cardiomyovasculopathy -Diagnosis and possible treatment of this novel rare disease entity-

新規疾患概念 中性脂肪蓄積心筋血管症の診断と治療法開発



平野 賢一 *Ken-ichi Hirano*

大阪大学大学院医学系研究科 中性脂肪学共同研究講座 特任教授  
Specially Appointed Professor,  
Department of Triglyceride Science,  
Graduate School of Medicine, Osaka University, Japan

大阪大学大学院医学系研究科 中性脂肪学共同研究講座 特任教授  
大阪大学 CNT研究室、中性脂肪研究センター  
Section editor for Orphanet J Rare Disease  
一般社団法人 中性脂肪学会 代表理事  
一般財団法人 栩野財団 代表理事

Specially appointed professor, Department of Triglyceride Science  
Laboratory for Cardiovascular Disease, Novel, Non-invasive, and Nutritional Therapeutics  
and Triglyceride Research Center, Graduate School of Medicine, Osaka University  
Section editor for Orphanet Journal of Rare Disease  
Representative Director, Society for Triglyceride Biology and Medicine  
Representative Director, the Tochino Foundation

中性脂肪蓄積心筋血管症 (Triglyceride deposit cardiomyovasculopathy, TGCV)は、2008年、我々が心臓移植待機症例から見出した新規疾患単位である (N Engl J Med. 2008)(ORPHA code: 565612)。TGCVでは、血管平滑筋細胞、心筋細胞などにおいてTG蓄積による脂肪毒性とエネルギー源である長鎖脂肪酸が供給されないためのエネルギー不全が生じる。

患者は、成人発症、治療抵抗性の心不全、びまん性のTG蓄積型動脈硬化を伴う冠動脈疾患に悩む。

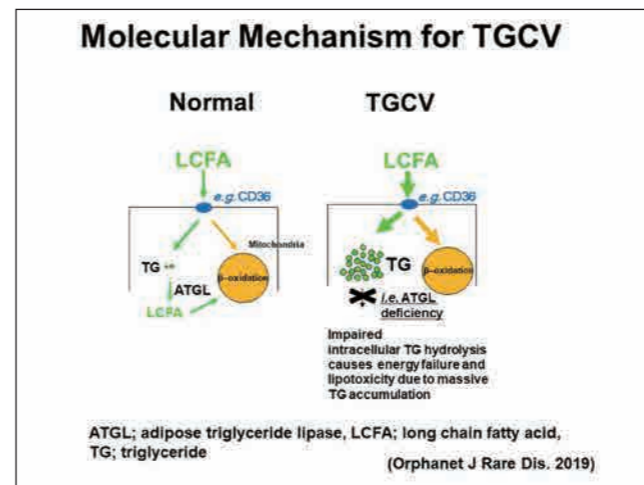
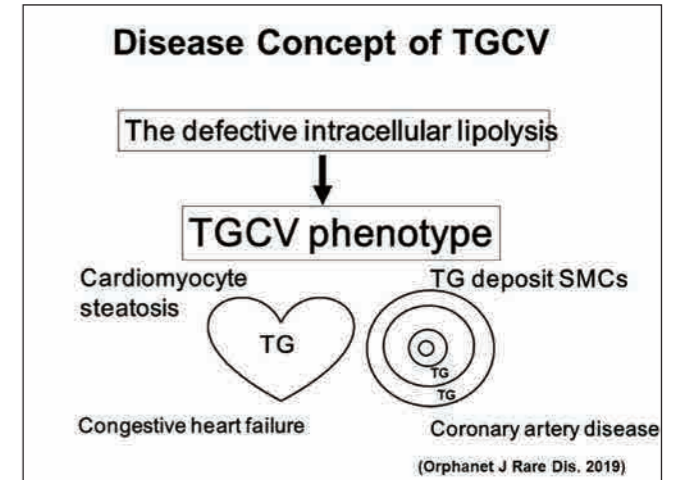
最新の累積診断数は336例、内 58例が既に死亡している。本講演では、厚生労働省や日本医療開発研究機構の難病事業として行ってきたTGCV診断基準2020の策定や2020年に先駆け指定医薬品となったTGCV治療薬 CNT-01(薬生薬審発 0619第1号)のアカデミア開発について述べる。

Triglyceride deposit cardiomyovasculopathy (TGCV) is a novel rare disease entity we found in Japanese patients with heart failure requiring cardiac transplantation (N Engl J Med. 2008). In TGCV, the defective intracellular lipolysis results in TG deposition and energy failure due to deficiency of long chain fatty acid, a major energy source of cardiomyocytes and vascular smooth muscle cells. TGCV patients suffer from adult-onset heart failure with cardiomyocyte steatosis and diffuse narrowing coronary artery disease with TG deposition which is resistant to standard remedies including cholesterol-lowering therapy and percutaneous coronary intervention with drug-eluting stents. Since 2009, we launched the Japan TGCV study group in order to develop diagnostic criteria and specific treatments, supported by research grants for rare diseases from the Ministry of Health, Labour, and Welfare (MHLW) of Japan, and the Japan Agency of Medical Research and Development. In 2019, TGCV was encoded as a new orphan disease in the Orphanet (ORPHA code: 565612). The cumulative patient number so far diagnosed in Japan is 336. Fifty-eight of them have already died, indicating high risk profile. As similar to those with other orphan diseases, TGCV patients have been suffering from the unawareness, un-diagnosis, and delayed diagnosis. In this lecture, we present the diagnostic criteria 2020 of TGCV to facilitate the diagnosis inside and outside Japan and academia-initiated development for a drug for TGCV (coded as CNT-01), which was recently assigned as a pioneering drug through "SAKIGAKE Designation System" of MHLW. We look forward to global collaboration to save TGCV patients.

### Triglyceride Deposit Cardiomyovasculopathy (TGCV, ORPHA code: 565612)

- Discovered in Japanese patients who had been waiting for heart transplantation
- Accumulation of TG in the heart and coronary arteries
- May be found in intractable heart failure/cardiomyopathy/coronary artery disease

Hirano K, et al. N Engl J Med. 2008. Eur Heart J. 2014. 2015. Int J Cardiol. 2015. Nihon Naka-gakkashi. 2017. Diabetes Care. 2019. Orphanet J Rare Dis. 2019. JAMA Netw Open. 2020. Heart. 2020



### Diagnostic Criteria 2020 for TGCV

Ann Nucl Cardiol 2020; 6 (1): 96-104. Kobayashi et al. — 101 —  
Diagnostic Criteria 2020 for TGCV

Table 1 Diagnostic Criteria 2020 for triglyceride deposit cardiomyovasculopathy

Items	Clinical findings
1. Essential items	Impaired LCFA metabolism or TG deposition in myocardium
	1) Decreased washout rate (<10%) in myocardial <sup>18</sup> F-BMIPP SPECT
	2) Myocardial TG deposition by biopsy specimens (a)
	3) Myocardial TG deposition by CT or MR spectroscopy
2. Major items	1) Decreased left ventricular ejection fraction (<40%)
	2) Diffuse narrowing of coronary arteries documented by CAG and/or coronary CT angiography (b)
	3) Typical Jordan's anomaly (apparent vasculi >1 μm in size) of polymorphonuclear leucocytes in peripheral blood smear (c)

Diagnosis  
Definite TGCV: One or more essential items and one or more major items are met.  
Probable TGCV: At least one essential item is met.  
Supportive items (d)  
1) Diabetes mellitus (e)  
2) Hypothyroidism

(The Japan TGCV study group)

