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REVIEW ARTICLE−DISEASE DISCOVERED IN JAPAN AND THE ROLE OF NUCLEAR CARDIOLOGY

Diagnostic Criteria and Severity Score for Triglyceride Deposit Cardiomyovasculopathy

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Abstract

Triglyceride deposit cardiomyovasculopathy (TGCV) is a rare and intractable disease, first reported in Japanese patients with congestive heart failure (HF) requiring heart transplant. TGCV is characterized by the excessive accumulation of triglyceride (TG) in cardiomyocytes and vascular smooth muscle cells, which leads to coronary artery disease, HF, and arrhythmia. In TGCV, long-chain fatty acid (LCFA), a major energy source for the normal heart, accumulates as TG in cytoplasmic lipid droplets. In 2009, we launched the Japan TGCV study group to elucidate the pathophysiology of TGCV and have developed diagnostic procedures along with specific treatment. Single-photon emission computed tomography (SPECT) with iodine-123-β-methyl iodophenyl-pentadecanoic acid (BMIPP), a radioactive analogue for LCFA, is a useful diagnostic tool to detect impaired myocardial LCFA metabolism in TGCV. Since we posted the latest version of diagnostic criteria including the myocardial washout rate of BMIPP in SPECT in 2016, we have identified 138 patients with TGCV, 27 of whom have died. More recently, we developed a TGCV severity score consisting of specific questionnaires in order to assess symptoms and activities of daily living in patients with TGCV.

Keywords: Diagnostic criteria, Iodine-123-β-methyl iodophenyl-pentadecanoic acid, Severity score, TGCV questionnaire, Triglyceride deposit cardiomyovasculopathy, Washout rate
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Triglyceride deposit cardiomyovasculopathy (TGCV) is a novel disease concept that was discovered in Japanese cardiac transplant recipients (1). Patients with TGCV have severe heart failure (HF), arrhythmia, and coronary artery disease (CAD) (1-3). Based on our clinical studies, the diagnostic criteria for TGCV have been reported by the Japan TGCV study group, where the increasing importance of iodine-123-β-methyl iodophenyl-pentadecanoic acid (BMIPP) single-photon emission computed tomography (SPECT) has been clarified. Here, we provide current information on TGCV and the activities of the Japan TGCV study group.

Definition, classification, and pathophysiology of TGCV

The phenotype of TGCV was primarily reported in patients with severe HF and genetic mutations of adipose triglyceride lipase (ATGL) (1), which is a rate-limiting enzyme for intracellular hydrolysis of TG and release of long-chain fatty acid (LCFA) as a major cardiac energy source (4). TGCV is characterized by excessive TG accumulation in both myocardium and coronary arteries, and the subtypes are classified into primary TGCV (P-TGCV, with ATGL mutations) and idiopathic TGCV (I-TGCV, without ATGL mutations) (5). Genetic causes and etiologies of the latter are unknown. I-TGCV was initially identified in the autopsied study with diabetic patients (6) and we recently reported that ATGL activities in peripheral leukocytes were markedly reduced in some patients with I-TGCV (7). In TGCV, abnormal metabolism of intracellular TG and LCFA such as ATGL dysfunction leads to lipotoxicity and energy failure in affected cells and tissues, resulting in HF, CAD, and arrhythmia (3, 7).

Latest version of diagnostic criteria for TGCV and number of patients identified

In September 2016, we posted the latest version of diagnostic criteria for TGCV (8). As shown in Table 1, these criteria include 2 major items (2 points each) and 2 minor items (1 point each). Four points or more and 3 points indicate definite and probable TGCV, respectively. The major items refer to TG deposition in myocardium and coronary arteries, which is the pathological basis of TGCV. The two minor items are Jordans' anomaly (9, 10) and diabetes mellitus. To date, 138 patients with TGCV have been identified from 7 institutes and hospitals in Japan. Unfortunately, 27 patients have died. These data indicate that TGCV is a rare and intractable

Table 1 Diagnostic criteria for triglyceride deposit cardiomyovasculopathy

Items	Clinical findings	
1. Major items (2 points)	1.1 Myocardial TG deposition or impaired LCFA metabolism	
	At least one of the following:	
	1) Myocardial TG deposition by biopsy specimens (a)	
	2) Myocardial TG deposition by MR spectroscopy	
	3) Decreased washout rate (<10%) of BMIPP	
	1.2 Diffuse narrowing coronary arteries demonstrated by CAG, CT angiography (b)	
2. Minor items (1 point)	2.1 Jordans' anomaly (apparent vacuoles of about 1 micrometer in size) of polymorphonuclear leucocytes in peripheral blood smear (c)	
	2.2 Diabetes mellitus (d)	
Diagnosis of TGCV	(1) 4 points or more	Definite TGCV
		Primary TGCV, if with ATGL mutation
		Idiopathic TGCV, if without ATGL mutation (e)
	(2) 3 points	Probable TGCV
		If ATGL mutations confirmed, definite TGCV considered

(a) For tissue TG contents examination, frozen sections with osmium fixation, but not paraffin sections, should be used for prevention of lipid elution
(b) The presence or absence of a significant stenosis is not considered
(c) For difficult cases, May-Giemsa staining slides of peripheral blood smear will be evaluated by the Japan TGCV study group
(d) According to the diagnostic criteria of DM by the Japan Diabetes Society
(e) If no opportunity for genetic analyses for ATGL (i.e ., deceased cases), the Japan TGCV study group can judge under clinico-pathological datasets
Please feel free to contact our study group (E-mail: info@tgcv.org)

* Abbreviations: ATGL: adipose triglyceride lipase, BMIPP: iodine-123-β-methyl iodophenyl-pentadecanoic acid, CAG: coronary angiography, CT: computed tomography, LCFA: long chain fatty acid, MR: magnetic resonance, TG: triglyceride, TGCV: Triglyceride deposit cardiomyovasculopathy

(Note: English version of table has been provided by the authors)

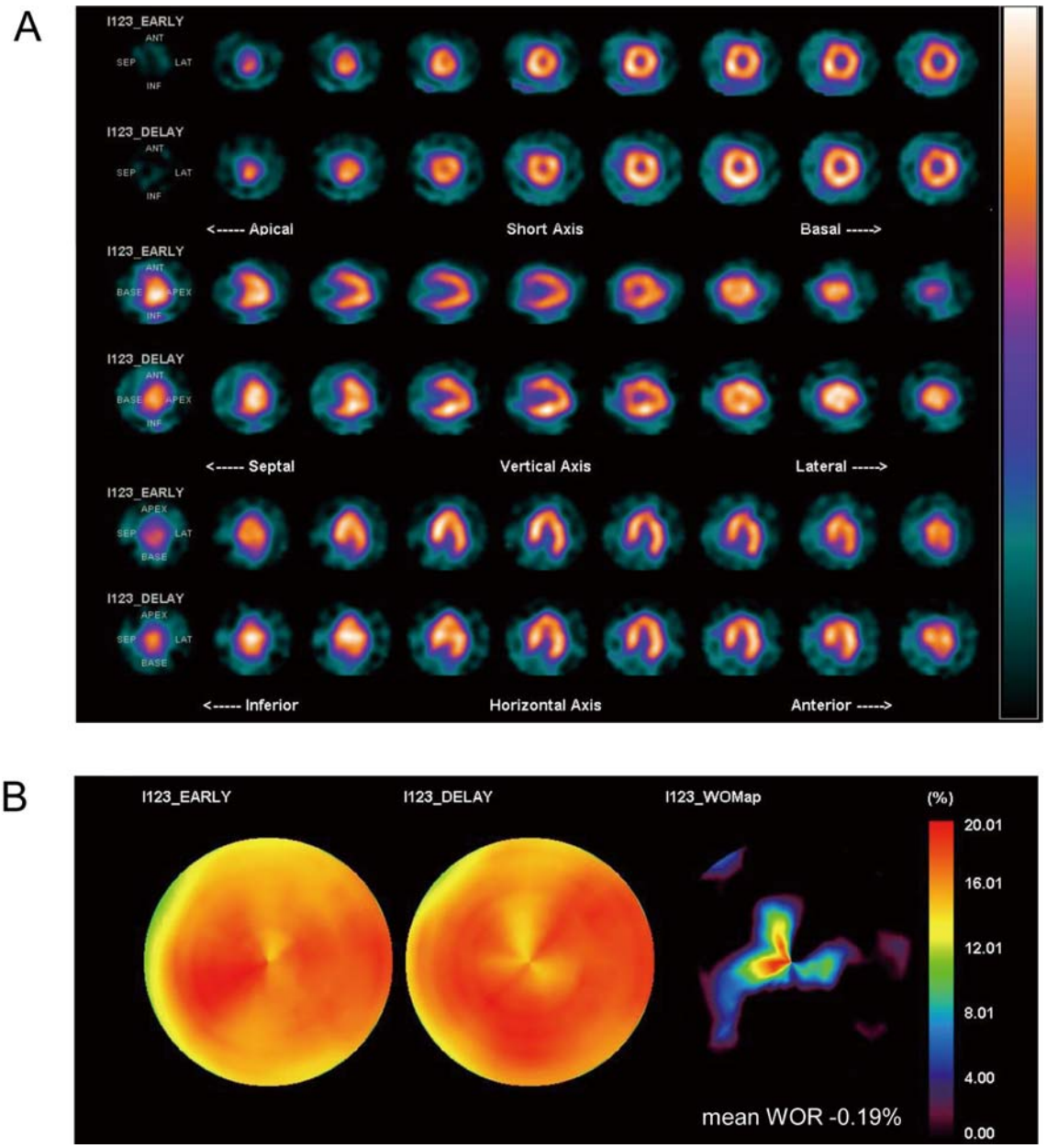

Fig. 1 ^{123}I-BMIPP SPECT images in a TGCV patient.
A: Short-axis, vertical long-axis, and horizontal long-axis tomographic images.
B: Displays on a circumferential polar plot.

cardiovascular disease.

Significance of washout rate of BMIPP-SPECT in the diagnosis of TGCV

BMIPP-SPECT is used to evaluate metabolism of LCFA in cardiomyocytes (11). LCFA is an essential energy source of the normal heart. After LCFA is taken up by cardiomyocytes, it is either synthesized to TG or being underwent beta oxidation to be energy-utilized, and BMIPP takes similar intracellular dynamics (11, 12). However, in patients with TGCV, once LCFA is pooled as TG, it remains inside the cell without being hydrolyzed (3). Hence, patients with TGCV have markedly decreased washout rate (WOR) of BMIPP (13), which is unrelated to local myocardial uptake abnormality (Fig. 1). In order to calculate the WOR of BMIPP, acquisition of delayed imaging up to 240 minutes after intravenous administration of tracer is performed in addition to early imaging at less than 30 minutes. After constructing polar map displays from short-axis, early and delayed SPECT imaging, WOR is calculated from the mean tracer counts (13). BMIPP-SPECT for diagnosis of TGCV should be avoided in the acute phase of acute coronary syndrome, such as acute myocardial infarction and unstable angina pectoris, because both washout and fill-in of BMIPP in delayed imaging have been reported in the acute phase of myocardial ischemia (14-16), thereby impeding accurate evaluation of TGCV.

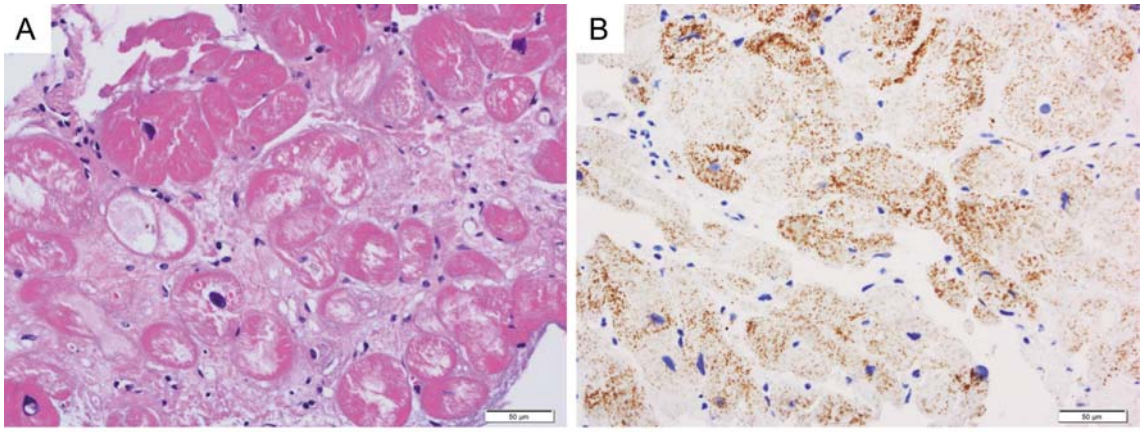

Fig. 2 Histopathological examinations demonstrate the accumulation of TGs in the myocardium.
A: Histological section stained with hematoxylin and eosin (H&E).
B: Histological section stained with immunohistochemistry for PLIN 2.
Histopathological examinations of myocardial biopsy, surgically resected myocardium, and explanted heart directly demonstrate the accumulation of TG in the myocardium. For examination under light microscopy, the myocardial specimens are immediately fixed with 10% formalin, stored at room temperature, embedded in paraffin, cut into 4-μm sections and stained with H&E, and immunohistochemical staining is performed for perilipin 2. A histological section stained with H&E demonstrates many small vacuoles that are suggestive of prominent lipid droplets in the cytoplasm of cardiomyocytes (A) in a 62-year-old patient with idiopathic TGCV.

Detection of myocardial small lipid droplets

In some cases with TGCV, lipid droplets in cardiomyocytes are too small to be detected by lipid staining such as Oil red O. Hara et al. reported that the overexpression of perilipin (PLIN) 2, a lipid droplet maintenance protein, was a possible biomarker candidate in the context of lipid metabolism using fibroblasts from TGCV patients (17). Therefore, we can detect small lipid droplets as a PLIN 2 protein mass in cardiomyocytes (Fig. 2B), indicating that PLIN 2 may be a useful histological protein marker for cardiomyocyte steatosis.

Differential diagnosis of TGCV

It is important to differentiate TGCV from other cardiovascular diseases as follows: dilated cardiomyopathy, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, mitochondrial cardiomyopathy, alcoholic heart disease, metabolic myocardial disorders (e. g., Fabry disease, Pompe disease, and cholesteryl ester storage disease). Furthermore, because a mild reduction of BMIPP WOR was reported in chronic hemodialysis patients (18), it would be of interest to know whether TGCV phenotype might exist among patients with chronic kidney disease, as reported in our postmortem study (6).

Development of severity score for TGCV

In order to assess symptoms of this newly identified disease, we collected clinical symptoms through interviews with TGCV outpatients in the Osaka University Hospital. Based upon the information, we developed 2 sets of TGCV-specific questionnaires: One set is for symptoms (the upper panel in Table 2) and the other for activities of daily living (ADL) (the lower panel in Table 2).

The former includes 4 sections as follows: 1) ischemic heart symptoms, 2) arrhythmia symptoms, 3) heart failure or energy failure symptoms, and 4) peripheral symptoms. Each section includes 3-5 questions (Qs). The point for each answer ranges from 0 (Never) to 4 (Always) (please see the footnote of the upper panel). As shown in Table 2 with input example, if patient's answers are "Frequently", "Frequently", "Frequently", "Always" and"Frequently" for Qs1-5 in the first section, the points would be 3, 3, 3, 4 and 3, respectively. The subscore of this first section is total points of the five answers (=16 points). Other subscores are summed as the same as the first section. The severity score for symptoms is the total of subscores from four sections. Thus, TGCV severity score for symptoms would be 37 points in this input example.

The latter includes 6 sections as follows: 1) diet and cooking, 2) physical cleanliness, 3) excretion, 4) daily life movement/change of clothes, 5) light physical work, and 6) walking. Each answer is rated on a 4-point scale (0-On my own, 1- Slightly hard, 2- Very hard, 3-impossible) (please see the footnote of lower panel). As shown in the lower panel of Table 2, the severity score for ADL is summed as that for symptoms.

The significance of patient-reported outcomes has been acknowledged for the assessment of clinical trials and development of therapy (19, 20). Although it is necessary to examine the reliability and validity of the questionnaires and

Table 2 Severity Scores for Triglyceride Deposit Cardiomyovasculopathy (TGCV)

1) Questionnaire for symptoms

			Input example		
Clinical classification	No	Questions for Symptoms	Point	Subscore	Severity score
Section1 Ischemic heart symptom	Q1	Do you have chest pain (angina pain) and heaviness and squeezing in the chest?	3	16	37
	Q2	Have you taken sublingual nitroglycerin?	3		
	Q3	Have you had the following symptoms before you have chest pain? (feeling like choking; feeling that something is welling up in the throat; feeling that your back is getting hot, etc.)	3		
	Q4	Have you experienced symptoms of the chest, dyspnea, or shortness of breath, regardless of whether there is exertion or you are at rest?	4		
	Q5	Have you had pain which spreads to the back, shoulders, or jaw?	3		
Section2 Arrhythmia symptom	Q6	Have you experienced palpitations such as a feeling of pounding or fluttering to your heartbeat?	3	3	
	Q7	Have you experienced that your pulse is suddenly racing?	0		
	Q8	Have you ever felt that your pulse is missed or slow?	0		
Section3 Heart failure, energy failure symptom	Q9	Do you feel easily fatigued, general malaise, etc.?	4	12	
	Q10	Have you experienced edema on your face, hands, or feet?	4		
	Q11	Have you felt that your breathing is better sitting up rather than lying down at night?	0		
	Q12	Have you ever felt weak in the hands or feet (i.e., feel heavy in the arms or legs)?	3		
	Q13	Do you always feel that your temperature is low?	1		
Section4 Peripheral symptom	Q14	Have you ever felt that your fingers or toes get too cool (cold sensation in the extremities)?	1	6	
	Q15	Do you have numbness in the fingers or toes or your entire hands or feet?	0		
	Q16	Have you ever felt dullness in both fingers and toes or your entire hands and feet?	0		
	Q17	Have you ever had a cramp in your leg or toe?	3		
	Q18	For respondents receiving diabetes treatment - have you ever experienced a hypoglycemic episode?	2		

Point definition for patients' answers: O, never; 1, rarely; 2, sometimes; 3, frequently; 4, always.

2) Questionnaire for Activities of Daily Living (ADL)

			Input example		
Classification	No.	Questions for ADL	Point	Subscore	Severity score
Section1 Diet, cooking	Q1	Can you prepare your meals including cooking?	1	4	23
	Q2	Can you have a meal by yourself?	0		
	Q3	Can you open a can or open the lid of a plastic bottle by yourself?	1		
	Q4	Can you straighten up and wash the dishes and clear the table after a meal?	2		
Section2 Physical cleanliness	Q5	Can you take a bath or shower by yourself?	2	2	
	Q6	Can you reach to wipe your whole body by yourself?	0		
	Q7	Can you do facial cleansing or toothbrushing by yourself?	0		
	Q8	Can you do your hair (using a tool including comb and hairdryer) by yourself?	0		
Section3 Excretion	Q9	Can you go to the bathroom without difficulty by yourself in the daytime?	0	0	
	Q10	Can you go to the bathroom by yourself at night?	0		
	Q11	Can you get up from a toilet seat by yourself?	0		
	Q12	Can you take your clothes off and put them on by yourself in a bathroom?	0		
Section4 Daily lifemovement・change of clothes	Q13	Can you hang out the laundry and take in it?	0	5	
	Q14	Can you change your clothes by yourself?	1		
	Q15	Can you put on your shoes (footwear) by yourself?	2		
	Q16	Can you clean your room?	2		
Section5 Light laborious work	Q17	Can you walk in your house without restrictions?	0	6	
	Q18	Can you carry heavy shopping bag, baggage and bag in your hand or on your shoulder?	3		
	Q19	Can you go shopping or walking alone?	1		
	Q20	Can you perform light exercise in a room (e.g., gymnastics done to commands and music on the radio [television])?	2		
Section6 Walk	Q21	Can you walk around 100 to 200 m on flat land?	1	6	
	Q22	Can you walk rapidly (in step with a healthy person)?	1		
	Q23	Can you walk on a slope without difficulty?	2		
	Q24	Can you go up and down the stairs to the second floor?	2		

Point definition for patients' answers: O, on my own; 1, slightly hard; 2, very hard; 3, impossible.
(Note: English version of table has been provided by the authors)

to compare the results with those of other subjective instruments including the Minnesota Living with Heart Failure questionnaire (21) and the 36-item Short Form (22), we believe that the developed specific severity score will be useful in clinical trials and studies of patients with TGCV.

Issues to be resolved

Following points are important focus for future researches:

1. Etiologies and genetic causes of I-TGCV

Our previous report (23) indicated that heterozygous carriers of ATGL mutation did not show apparent cardiovascular or neurological symptoms, compared with non-carriers. The mechanism underlying down-regulation of ATGL activities of I-TGCV and possible involvement of other lipases and related enzymes is of significance to elucidate.

2. As mentioned recently (10), vacuolar formation was observed in less than 10% of leukocytes in I-TGCV, in contrast to P-TGCV with almost all leucocytes manifesting Jordans' anomaly (24). Any screening methods to detect Jordans' anomaly and measure ATGL protein in I-TGCV need to be developed.

3. Continued validation of diagnostic criteria for TGCV

The number of TGCV patients is still limited. During the course of elucidation of all issues above, diagnostic criteria should be kept updated.

Finally, the Japan TGCV study group recently reported that medium-chain fatty acids had a therapeutic effect in a mouse model for TGCV (25) and have already finished phase I and I/IIa clinical trials (NCT 02502578, NCT 02830763). A next-phase clinical trial is now in preparation.

Author contribution

HM, CH, YI, ML, KK, and KH wrote the manuscript. HM, YI, MaH, TI, and HN are members of the task force on diagnostic criteria. CH, HM, and ML are members of the task force on severity score. YN, JK, ES, YaN, KS, SK, KK, KS, TI, TA, and KK provided patient information and contributed to the discussion. KH is the principal investigator for the Japan TGCV study group.

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Conflicts of interest

KH received grants from Nihon Medi-Physics Co. Ltd.

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CORRECTION

DISEASES DISCOVERED IN JAPAN AND THE ROLE OF NUCLEAR CARDIOLOGY — REVIEW ARTICLE

Imaging Modalities for Triglyceride Deposit Cardiomyovasculopathy

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This paragraph needs to be corrected. (p 97, right column, 25-30 lines)

1. Triglyceride accumulation in peripheral polynuclear leukocytes

Vacuolar degeneration (called Jordans' anomaly) in polymorphonuclear leukocytes can be observed on blood smears (May Giemsa staining) (19, 20). These vacuoles are positive for lipid staining such as oil red O.

The corrected paragraph is as follows.

1. Triglyceride accumulation in peripheral polynuclear leukocytes

Vacuolar degeneration (called Jordans' anomaly) in polymorphonuclear leukocytes can be observed on blood smears (May Giemsa staining) (19, 20).

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