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Triglyceride deposit cardiomyovasculopathy: How to recognise a new disease entity

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Introduction

"The real voyage of discovery consists not in seeking new landscapes, but in having new eyes" – Marcel Proust.

New perspectives can require a paradigm shift, then innovative concepts can arise from incidental but penetrating insights. A new disease entity might require new diagnostic and conceptual approaches before achieving general acceptance. The establishment of diagnostic criteria is based on experience and essential differentiation from similar pathologies and secondary conditions. Essential pathophysiological and genetic approaches might lead to novel therapeutic methods that could rescue patients from lethal events.

Hirano et al. identified triglyceride deposit cardiomyovasculopathy (TGCV) in a patient who received a heart cardiac transplant in Japan during 2008 [1, 2]. Microscopy revealed atherosclerotic triglyceride, rather than cholesterol deposits, in the coronary arteries, and numerous vacuoles in cardiomyocytes of the explanted heart. Genetic analysis discovered that the patient harboured a mutation in the adipose triglyceride lipase gene. One established cause of TGCV is a genetic deficiency of adipose triglyceride lipase that plays a key role in intracellular triglyceride hydrolysis. Thus, TGCV was encoded as a rare cardiovascular disorder in Orphanet (ORPHA code: 565612) [3]. This editorial discusses how to recognise and diagnose TGCV using current methods and provides some suggestions to help understand this rare disease entity.

TGCV and atherosclerosis

The principal disorder in TGCV is defective intracellular lipolysis, which causes excessive triglyceride accumulation in the myocardium and coronary artery vascular smooth muscle cells, leading to heart failure and coronary artery disease with a poor prognosis.
The total number of patients diagnosed with TGCV in Japan between 2008 and 2014 was < 10 according to a report published by the Japan TGCV study group [4]. Thereafter, the number increased to 226, among whom, 45 were deceased by the end of 2019, indicating a high-risk profile. The rapid increase in the number of patients might have been partly due to the fact that the diagnostic criteria have piqued public and cardiologist interest in enhancing awareness of TGCV. The prevalence of TGCV awareness is low outside of Japan. Diffuse atherosclerotic lesions associated with multivessel coronary artery disease should be carefully excluded by identifying coronary artery narrowing using coronary CT and coronary angiography. Atherosclerotic lesions due to familial hypercholesterolemia can be differentiated by serum lipid profiles. Other disease entities that require exclusion include [4] hypertrophic, dilated, arrhythmogenic right ventricular, diabetic, and mitochondrial cardiomyopathies, alcoholic heart disease, metabolic myocardial disorders such as Fabry, Pompe, Danon, mitochondrial and cholesteryl ester storage diseases, and a CD36 deficiency, as well as a drug-induced or dialysis-associated carnitine deficiency, and excessive epicardial fat deposition.

Prognosis of TGCV and haemodialysis

Onishi et al. reported the prevalence and prognosis of TGCV among patients on haemodialysis in this issue of Heart [5]. The prevalence of nonfatal myocardial infarction, nonfatal stroke or cardiovascular death for patients with definitive TGCV was 53% in contrast to patients without TGCV (9%). The 20% frequency of definitive TGCV in patients with haemodialysis and suspected of having coronary artery disease might have been partly attributed to author selection bias for ^{123}I-BMIPP imaging and a diagnosis of diffuse coronary artery narrowing. Thus, whether the frequency of TGCV can be extrapolated to patients on haemodialysis in other communities and nations is not clear. In addition, their study was based on diagnostic criteria defined in 2016, when myocardial triglyceride deposition or impaired LFCA metabolism and diffuse coronary narrowing were considered as major components (2 points each), whereas the Jordan anomaly and diabetes were considered as minor components (1 point each). Scores of ≥ 4 and 3 were taken as definitive and probable TGCV, respectively. The 2020 diagnostic criteria for TGCV include the modifications discussed below (Table 1). However, their diagnosis of definitive TGCV would not be changed even with the new criteria, and the present study suggests that a diagnostic combination of ^{123}I-BMIPP and diffuse narrowing of coronary arteries is effective for the diagnosis.

^{123}I-BMIPP fatty acid imaging

Long-chain fatty acids (LCFA) comprise the major energy source of the normally contracting heart. They are incorporated into the cellular triglyceride pool after uptake into cardiomyocytes (Figure 1A), where enzymes such as adipose triglyceride lipase, hydrolyse triglycerides. Released fatty acid is subsequently oxidised in the mitochondria to produce adenosine triphosphate. Metabolic processes can be visualised using the unique radiotracer, β-methyl-iodophenylpentadecanoic acid (^{123}I-BMIPP). This tracer has been widely applied in Japan since the Ministry of Health and Welfare approved ^{123}I-BMIPP with wide indications for cardiac diseases in1993. After uptake into

myocytes, ^{123}I-BMIPP is transferred to the triglyceride pool, then to mitochondria, but it is not immediately metabolised by β oxidation, due to having branched structures in the beta position. It is therefore regarded as a retention-type radiotracer that undergoes slow α oxidation followed by β oxidation, which differs from LCFA that are a major cardiac source of energy. However, slow clearance from the heart is convenient for nuclear single-photon emission computed tomography (SPECT) imaging. Images are obtained early (15 minutes) and late (3–4 hours) after intravenous injection of the tracer to calculate washout rates. The average washout rate in 3 hours is 10%–30% in coronary artery disease and even under normal conditions. Thus, a low washout rate (< 10%) can be an important indicator of TGCV metabolism. While reduced ^{123}I-BMIPP clearance might have a diagnostic role in TGCV, BMIPP kinetics are not yet fully understood and are considered to be a composite of back diffusion, α and β oxidation, and intermediate metabolites. Since washout can vary depending on the algorithm used to calculate it, a standardised method applicable to heterogeneous distribution and focal defects should be investigated from a technological viewpoint to determine the optimal diagnostic threshold. Figure 1B and C shows typical ^{123}I-BMIPP clearance in patients with and without TGCV.

New diagnostic criteria for TGCV

The revised 2020 diagnostic criteria conformed to this underlying pathophysiology (Table 1) [4]. The essential diagnostic criteria comprise metabolic evidence of very slow or absent triglyceride clearance from the heart determined as ^{123}I-BMIPP washout rates on myocardial SPECT [6], direct histological evidence from biopsy specimens identified in the initial report about the patient [1], and evidence of triglyceride deposits determined by X-ray computed tomography (CT) or nuclear magnetic resonance (NMR) spectroscopy. The essential items associated with evidence of triglyceride deposition in the new guidelines are emphasised, and heart failure has been added. In addition, the major criteria include reduced left ventricular contractility associated with heart failure, which reflects the experiences of patients with TGCV, during which atypical courses might arise. Diffuse narrowing of coronary arteries with triglyceride deposition is also a feature [7]. The Jordan anomaly in peripheral blood smears is also diagnostic, although neutral lipid storage disease with ichthyosis, and a carnitine palmitoyltransferase deficiency can also cause this anomaly. Primary and idiopathic TGCV can be differentially diagnosed based on the presence or absence, respectively, of a typical Jordan anomaly. Since TGCV cannot be diagnosed with conventional serum triglyceride, cholesterol profiles, and body mass index, the new guidelines should help physicians to diagnose TGCV effectively.

What is the next step?

A new perspective and diagnostic procedures might be required to diagnose new disease entities. However, the first step is to become aware of a disease and try to visualise it. Even when diagnosed by contemporary techniques, therapeutic intervention will be the next important step. In this context, glyceryl decanoate (tricaprin) has been investigated as a nutritional therapeutic agent [8], as this medium-chain fatty acid eliminates myocardial triglyceride deposition. A diagnosis of TGCV might be more easily promoted using ^{123}I-BMIPP in Japan. However, ^{123}I-BMIPP might also be useful for research applications elsewhere, and the feasibility of approaches using X-ray CT and NMR spectroscopy should also be investigated to extend diagnostic capabilities worldwide. Accumulated experience with TGCV is definitely important to determine the next steps.

Table 1 Diagnostic criteria 2020 for triglyceride deposit cardiomyovasculopathy

Items Clinical findings
1. Essential items Impaired LCFA metabolism or triglyceride deposition in myocardium 1) Decreased washout rate (<10%) in myocardial ^{123}I-BMIPP SPECT 2) Myocardial triglyceride deposition by biopsy specimens (a) 3) Myocardial triglyceride 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 Jordans' anomaly (apparent vacuoles >1μm 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) Haemodialysis
(a) For tissue triglyceride 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) These items are commonly present according to autopsy heart analysis and small-scale cohort analysis performed by the Japan TGCV Study Group but not proven to have diagnostic accuracy or causal relationship.
(e) According to the diagnostic criteria of diabetes mellitus by the Japan Diabetes Society.

If imaging protocols for ^{123}I-BMIPP myocardial scintigraphy, cardiac CT and cardiac MR spectroscopy are needed, contact Japan TGCV Study Group (E-mail: info@tgcv.org)

Abbreviations: CAG, coronary angiography; CT, computed tomography; ^{123}I-BMIPP, iodine-123-β-methyl-iodophenyl-pentadecanoic acid; LCFA, long chain fatty acid; MR, magnetic resonance; SPECT, single-photon emission computed tomography; TGCV, triglyceride deposit cardiomyovasculopathy

Cited with permission from Ann Nuclear Cardiol [4].

Initial version of the diagnostic criteria: Ann Nucl Cardiol 2018;4:94-100

Figure

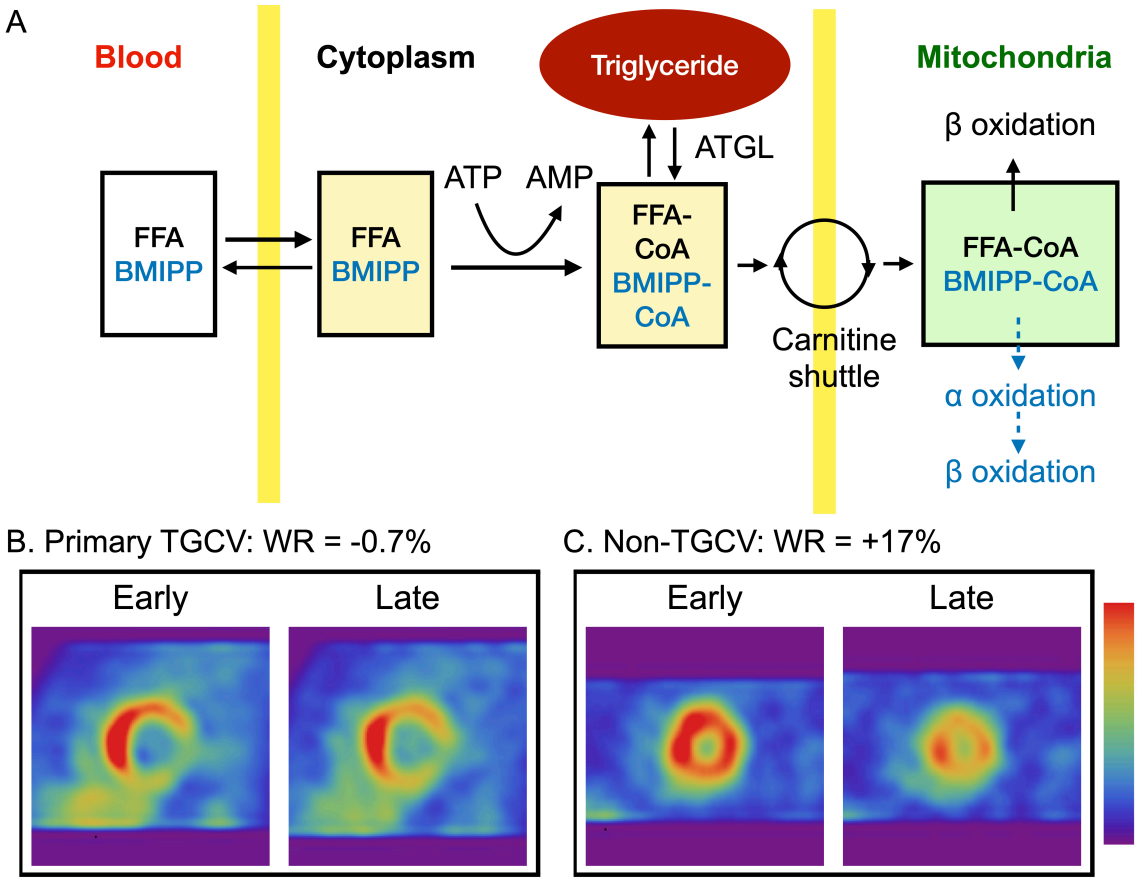

Figure 1

Metabolism of free fatty acid and ^{123}I-BMIPP and typical short-axis ^{123}I-BMIPP images in patients with and without TGCV.

Free fatty acid (FFA) and ^{123}I-BMIPP metabolism (A). Early (15 minutes) and late (3 hours) ^{123}I-BMIPP mid short-axis images of 35- and 58-year-old men with primary TGCV (B) and aortic regurgitation (C), respectively. Actual range of ^{123}I-BMIPP activity is shown as standardised to maximum early count of 100%, and decay for 3 hours is corrected. Uptake is similar in the early and late images of patient with TGCV (B), but reduced in late image of patient without TGCV (C). Calculated washout rates of ^{123}I-BMIPP from whole heart counts were -0.7% and 17%, respectively. Original patient information was provided courtesy of Professor Ken-ichi Hirano, Osaka University, Japan.

Abbreviations: AMP, adenosine monophosphate; ATGL, adipose triglyceride lipase; ATP, adenosine triphosphate; FFA, free fatty acid; TGCV, triglyceride deposit cardiomyovasculopathy.

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