






CASE REPORT

REVISED Case Report: Sustained mitochondrial damage in cardiomyocytes in patients with severe propofol infusion syndrome [version 2; peer review: 2 approved]

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Abstract

Introduction: Propofol infusion syndrome (PRIS) is rare but a potentially lethal adverse event. The pathophysiologic mechanism is still unknown.

Patient concerns: A 22-year-old man was admitted for the treatment of Guillain-Barré syndrome. On day six, he required mechanical ventilation due to progressive muscle weakness; propofol (3.5 mg/kg/hour) was administered for five days for sedation. On day 13, he had hypotension with abnormal electrocardiogram findings, acute kidney injury, hyperkalemia and severe rhabdomyolysis.







Diagnosis and interventions: The patient was transferred to our intensive care unit (ICU) on suspicion of PRIS. Administration of noradrenaline and renal replacement therapy and fasciotomy for compartment syndrome of lower legs due to PRIS-rhabdomyolysis were performed.


Outcomes: The patient gradually recovered and was discharged from the ICU on day 30. On day 37, he had repeated sinus bradycardia with pericardial effusion in echocardiography. Cardiac ¹⁸F-FDG PET on day 67 demonstrated heterogeneous ¹⁸F-FDG uptake in the left ventricle. Electron microscopic investigation of endomyocardial biopsy on day 75 revealed mitochondrial myelinization of the cristae, which indicated mitochondrial damage of cardiomyocytes. He was discharged without cardiac abnormality on day 192.


Conclusions: Mitochondrial damage in both morphological and functional aspects was observed in the present case. Sustained

Open Peer Review

Approval Status  

	1	2
version 2 (revision) 20 Jan 2022	 view	 view
version 1 16 Jul 2020	  view	  view

1. **Petra Fallier-Becker** , University Hospital of Tuebingen, Tuebingen, Germany
Susanne Haen, University of Tuebingen, Tuebingen, Germany

2. **Anja Karlstaedt** , Cedars Sinai Medical Center, Los Angeles, USA

Any reports and responses or comments on the article can be found at the end of the article.

mitochondrial damage may be a therapeutic target beyond the initial therapy of discontinuing propofol administration.

Keywords

mitochondria, arrhythmia, cardiac failure, Propofol

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Author roles: **Karasawa S:** Conceptualization, Writing – Review & Editing; **Nakada Ta:** Conceptualization, Data Curation, Formal Analysis, Writing – Review & Editing; **Mori N:** Visualization; **Daimon M:** Visualization; **Miyauchi H:** Visualization; **Kanai T:** Visualization; **Takano H:** Visualization; **Kobayashi Y:** Visualization; **Oda S:** Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

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First published: 16 Jul 2020, 9:712 <https://doi.org/10.12688/f1000research.24567.1>

REVISED Amendments from Version 1

We have added some sentences about how Propofol impairs carnitine palmitoyl transport activities and cardiac calcium dynamics, potentially affecting the oxidation of fatty acids. We have included a few sentences explaining the different findings between the past reports and the present study. In addition, we have made some minor changes to the text as suggested by the reviewers.

Any further responses from the reviewers can be found at the end of the article

Abbreviations

PRIS, propofol infusion syndrome; ^{18}F -FDG PET, ^{18}F -fluorodeoxyglucose positron emission tomography.

Introduction

Propofol is extensively used in the intensive care units (ICU) for sedation¹. Propofol infusion syndrome (PRIS) is widely recognized as an adverse event of this commonly used drug, but is rare and potentially lethal². The pathophysiologic mechanism is still unknown. However, mitochondrial damage is suggested to be a potential pathogenesis mechanism. Here we report a severe case of PRIS with evidence of mitochondrial damage in both morphological and functional aspects.

Case presentation

A 22-year-old man, who was a healthy university student with Japanese ancestry without preexisting medical and family history, experienced muscle weakness and was admitted for the treatment of Guillain-Barré syndrome. On day six, he required mechanical ventilation due to progressive muscle weakness; propofol (3.5 mg/kg/hour) was administered via a peripheral venous catheter for five days for sedation. On day 13, he had hypotension with abnormal electrocardiogram findings (ST elevation in II, III, and aV_p). Blood test revealed acute kidney

injury, hyperkalemia and severe rhabdomyolysis (serum creatinine phosphokinase 271,700 IU/L, normal range 68-287 IU/L). He was transferred to our ICU on suspicion of PRIS by excluding other diagnoses. Administration of noradrenaline via a central venous catheter (0.3 µg/kg/min) and hemodialysis were initiated, and fasciotomy by orthopedic surgeons under general anesthesia without propofol was required for compartment syndrome of lower legs due to PRIS-rhabdomyolysis. Noradrenaline was gradually reduced and terminated on day 15. He gradually recovered from cardiac and renal dysfunction according to echocardiography and blood tests and was discharged from the ICU on day 30. On day 37, he repeatedly presented sinus bradycardia and right bundle branch block in continuous electrocardiogram monitoring, eventually requiring temporary pacing via the intracardiac placement of a pacing wire, with a finding of pericardial effusion on echocardiography. Detailed examination including cardiac ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET) was conducted to evaluate whether these late-phase cardiac events were related to PRIS. Cardiac ^{18}F -FDG PET on day 67 demonstrated heterogeneous ^{18}F -FDG uptake in the left ventricle with a maximum Standardized Uptake Value(SUV) of 3.97 (Figure 1). Blood glucose level before imaging was 90mg/dL. Electron microscopic investigation of the endomyocardial biopsy, which was taken on day 75 to examine the cause of cardiac dysfunction, revealed abnormal findings in the mitochondria of the cardiomyocytes, including myelinization of the cristae (Figure 2), which was interpreted as mitochondrial damage. In addition, apoptotic myocytes were not observed. Since weakness of respiratory muscles and extremities muscles needed mechanical ventilation and rehabilitation, he was treated in the hospital for another 3 months. He was taken off the ventilator and transferred to another hospital on day 192 due to persisting muscle weakness, but with normal cardiac function without arrhythmia. Three-year follow-up revealed that he had normal cardiac function with normal activities of daily living.

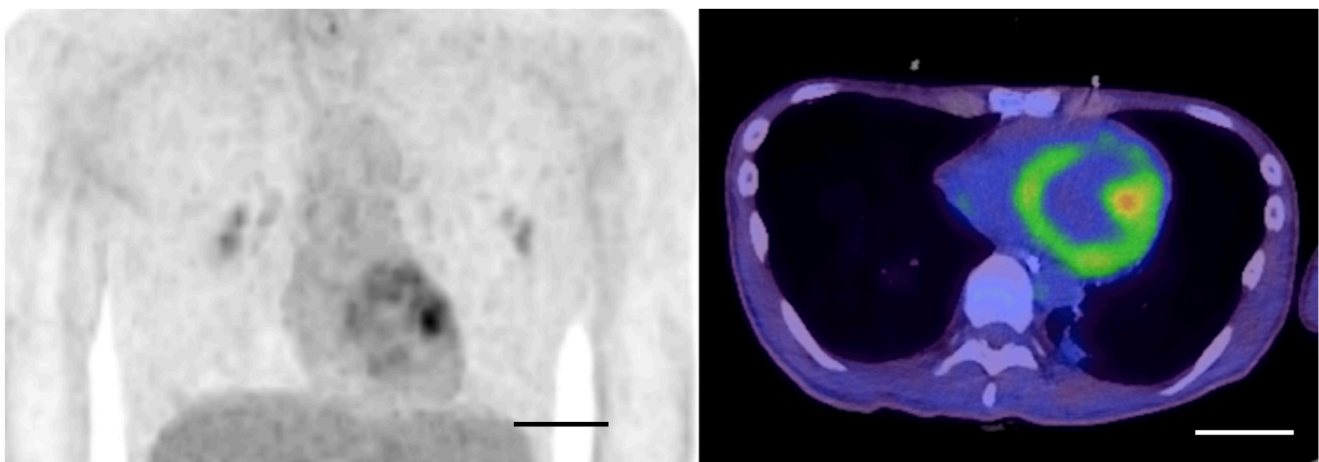


Figure 1. ^{18}F -fluorodeoxyglucose positron emission tomography. ^{18}F -fluorodeoxyglucose positron emission tomography showed heterogeneous ^{18}F -FDG uptake in left ventricle. Scale bar: 5cm.

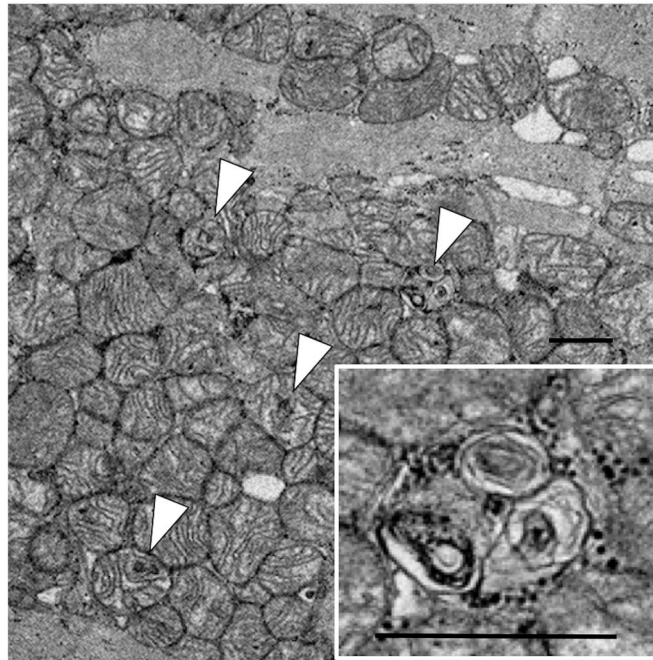


Figure 2. Electron microscopic investigation of endomyocardial biopsy. Electron microscopy revealed mitochondrial myelinizations of the cristae in cardiomyocyte. Arrows indicate cardiomyocytes with the mitochondrial injury. Scale bar: 1 μm .

Discussion and conclusions

Mitochondrial damage is suggested as a potential pathogenesis of PRIS²⁻⁴. Mitochondrial damage was observed as a morphological finding in an electron microscopic evaluation of the heart in an autopsy case of PRIS⁵. We found myelinization of the cristae in cardiomyocyte on day 75; however, similar findings were not observed in postmortem electron microscopical image of mitochondria of PRIS in the previous report⁵. Different clinical course and timepoints may alter mitochondrial conditions. The autopsy study measured blood levels of short-chain acylcarnitines, while we have no blood sample available for the measurement. Further studies measuring blood levels of short-chain acylcarnitines would strengthen the case results. Similarly, mitochondrial damage was observed in the endomyocardial biopsy two months after the onset in the present case. Mitochondrial damage can also be detected as a functional impairment of fatty acid utilization with alternatively increased glucose utilization⁶. Propofol is known to inhibit the effects of carnitine palmitoyl transferase 1 (CPT 1), which transports long-chain fatty acids into the mitochondria³. Thus, propofol potentially impairs carnitine palmitoyl transport activities and cardiac calcium dynamics, affecting the oxidation of fatty acids³. The uptake of a glucose analog (¹⁸F-FDG) in left ventricle on day 67 (Figure 1) in the present case implies a shift in the energy substrate of cardiomyocytes from fatty acid to

glucose, suggesting mitochondrial damage. To the best of our knowledge, this is the first to report a case of PRIS with evidence of mitochondrial damage in both morphological and functional aspects, which is the strength of this case report. The evidence of increased glucose uptake by ¹⁸F-FDG PET and mitochondrial damage by electron microscopic investigation was not repeatedly evaluated during the time-course but a single time-point (¹⁸F-FDG PET on day 67 and endomyocardial biopsy 75), which is a potential limitation. Additional timepoints data in future studies would reveal that these flux changes occur due to mitochondrial damage or pharmacologic modulation of key regulatory enzymes and transporters. Since the mitochondrial damage was detected 2 month later after PRIS onset, sustained mitochondrial damage may be a therapeutic target beyond the initial therapy of discontinuing propofol administration.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Consent

Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

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[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

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Version 2

Reviewer Report 08 March 2022

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Anja Karlstaedt 

Cedars Sinai Medical Center , Los Angeles, CA, USA

The authors have addressed all my concerns and appropriately revised the manuscript. I can confirm that the submission is at an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cardiology, Metabolism, Systems Biology, Computational modeling.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 27 January 2022

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Petra Fallier-Becker 

Institute of Pathology and Neuropathology, University Hospital of Tuebingen, Tuebingen, Germany

Susanne Haen

Institute of pathology and neuropathology, University of Tuebingen, Tuebingen, Germany

The revisions are appropriate.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pathology, Neuroscience, Electron Microscopy

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 27 November 2020

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Anja Karlstaedt 

Cedars Sinai Medical Center , Los Angeles, CA, USA

Karasawa *et al.* present a case report titled "Sustained mitochondrial damage in cardiomyocytes in patients with severe propofol infusion syndrome." The authors describe the case of a 22-year-old man of Japanese descent who developed a propofol infusion syndrome (PRIS) as a complication of his treatment of Guillain-Barre syndrome. PRIS is a rare syndrome with an unknown pathophysiologic mechanism, lack of specific signs and symptoms, and high mortality. Together these factors pose a challenge for clinicians to identify patients with potential PRIS and to provide treatment. The present case report may help other clinicians manage a patient with possible PRIS and allow future studies to elucidate the underlying molecular mechanisms causing the syndrome.

The authors present their case clearly and concisely. However, the report has several shortcomings, which should be addressed in a revision.

Major concerns

1. The authors need to provide quantifications for the ^{18}F -FDG PET imaging, including how they normalized their counts (e.g., brain, blood glucose level before and after the imaging). The PET image lacks a scale.
2. Additional information regarding the endomyocardial biopsy is required. The authors should comment if they observed apoptotic myocytes, which stages of morphological stages of mitochondrial degeneration they found (e.g., A to D), and potentially provide quantification.
3. The authors indicate in their introduction that "mitochondrial damage is suggested to be a potential pathogenesis mechanisms." Further, in the discussion and conclusions, the authors suggest that "Mitochondrial damage can also be detected as a functional impairment of fatty acid utilization with alternatively increased glucose utilization [Ref 6]."

Readers who are less familiar with PRIS or cardiac metabolism would benefit from a brief description of how propofol impairs carnitine palmitoyl transport activities and cardiac calcium dynamics, potentially affecting the oxidation of fatty acids. The shift in energy-providing substrates is an essential pathophysiological aspect of the case report and, in general, cardiac stress response. Additional descriptions and references will help readers to follow the author's rationale.

4. The authors need to differentiate their case presentation between mitochondrial damage at the structural level as supported by the histology and functional changes due to metabolic remodeling. Metabolic remodeling in the heart can precede structural changes (for reference see: References 1-5). ^{18}F -FDG PET imaging shows increased glucose utilization in the heart on day 67, and the authors provide evidence for mitochondrial structural damage at day 75. The authors correctly conclude that these results imply a shift from predominant fatty acid oxidation to glucose. However, the data are insufficient to conclude that these flux changes occur due to mitochondrial damage or pharmacologic modulation of key regulatory enzymes and transporters, without additional time points.
5. The authors state: "The evidence of mitochondrial damage by ^{18}F -FDG PET [...]" ^{18}F -FDG-PET imaging does not determine mitochondrial damage but measures glucose uptake. Please revise (for example: "The evidence of increased glucose uptake and mitochondrial damage by [...].")

Minor remarks and questions:

1. Did the authors observe any changes in the blood glucose level or glucose tolerance of the patient?
2. The authors may consider further quantification of mitochondrial degeneration in their tissue sample using markers for autophagy and apoptosis, e.g., BNIP3, FOXO3a, BCL-2, or OPA1.

References

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Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cardiology, Metabolism, Systems Biology, Computational modeling.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 16 Dec 2021

Satoshi Karasawa, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo, Japan

Thank you for taking your time to review and comment on our manuscript. Sorry for the delay in response due to COVID-19 pandemic.

1. The authors need to provide quantifications for the 18F-FDG PET imaging, including how they normalized their counts (e.g., brain, blood glucose level before and after the imaging). The PET image lacks a scale.

Response:

Thank you for the comment. According to the comment, we revised the sentence and scale.

Added (Case presentation):

Detailed examination including cardiac 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) was conducted to evaluate whether these late-phase cardiac events were related to PRIS. Cardiac 18F-FDG PET on day 67 demonstrated heterogeneous 18F-FDG uptake in the left ventricle with the maximum standardized uptake value (SUV) of 3.97. Blood glucose level before and after imaging was 90 mg/dL.

Added (Figure and Figure legends):

I added scale bar to the Figure1.

Figure1. 18F-fluorodeoxyglucose positron emission tomography.

18F-fluorodeoxyglucose positron emission tomography showed heterogeneous 18F-FDG

uptake in left ventricle. Scale bar: 5cm

2. Additional information regarding the endomyocardial biopsy is required. The authors should comment if they observed apoptotic myocytes, which stages of morphological stages of mitochondrial degeneration they found (e.g., A to D), and potentially provide quantification.

Response:

Thank you for the comment. According to the comment, we added a sentence in the Case presentation section. Since the sample preparation for electron microscope images could affect the morphological stages, we assume that we could not accurately estimate the morphological stage of mitochondrial degeneration.

Added (Case presentation):

Electron microscopic investigation of the endomyocardial biopsy, which was taken on day 75 to examine the cause of cardiac dysfunction, revealed abnormal findings in the mitochondria of the cardiomyocytes, including myelinization of the cristae (Figure 2), which was interpreted as mitochondrial damage. In addition, apoptotic myocytes were not observed.

3. The authors indicate in their introduction that "mitochondrial damage is suggested to be a potential pathogenesis mechanisms." Further, in the discussion and conclusions, the authors suggest that "Mitochondrial damage can also be detected as a functional impairment of fatty acid utilization with alternatively increased glucose utilization [Ref 6]." Readers who are less familiar with PRIS or cardiac metabolism would benefit from a brief description of how propofol impairs carnitine palmitoyl transport activities and cardiac calcium dynamics, potentially affecting the oxidation of fatty acids. The shift in energy-providing substrates is an essential pathophysiological aspect of the case report and, in general, cardiac stress response. Additional descriptions and references will help readers to follow the author's rationale

Response:

Thank you for the comment. According to the comment, we added a reference and sentences in the Discussion and Conclusions.

Added (Discussion and Conclusions): :

Propofol is known to inhibit the effects of carnitine palmitoyl transferase 1 (CPT 1), which transports long-chain fatty acids into the mitochondria³. Thus, propofol potentially impairs carnitine palmitoyl transport activities and cardiac calcium dynamics, affecting the oxidation of fatty acids.

4. The authors need to differentiate their case presentation between mitochondrial damage at the structural level as supported by the histology and functional changes due to metabolic remodeling. Metabolic remodeling in the heart can precede structural changes (for reference see: References 1-5). 18F-FDG PET imaging shows increased glucose utilization in the heart on day 67, and the authors provide evidence for mitochondrial structural damage at day 75. The authors correctly conclude that these results imply a shift

from predominant fatty acid oxidation to glucose. However, the data are insufficient to conclude that these flux changes occur due to mitochondrial damage or pharmacologic modulation of key regulatory enzymes and transporters, without additional time points.

Response:

Thank you for the comment. According to the comment, we added sentences in the Discussion and Conclusions.

Added (Discussion and Conclusions):

The evidence of mitochondrial damage by 18F-FDG PET and electron microscopic investigation was not repeatedly evaluated during the time-course but a single time-point (18F-FDG PET on day 67 and endomyocardial biopsy 75), which is a potential limitation. Additional timepoints data in future studies could reveal that shifts from predominant fatty acid oxidation to glucose occur due to mitochondrial damage or pharmacologic modulation of key regulatory enzymes and transporters.

5. The authors state: "The evidence of mitochondrial damage by 18F-FDG PET [...]. 18F-FDG-PET imaging does not determine mitochondrial damage but measures glucose uptake. Please revise (for example: "The evidence of increased glucose uptake and mitochondrial damage by [...].")

Response:

According to the comment, we revised the sentence.

Previous (Discussion and Conclusions):

The evidence of mitochondrial damage by 18F-FDG PET and electron microscopic investigation was not repeatedly evaluated during the time-course but a single time-point (18F-FDG PET on day 67 and endomyocardial biopsy 75), which is a potential limitation. Since the mitochondrial damage was detected 2 month later after PRIS onset, sustained mitochondrial damage may be a therapeutic target beyond the initial therapy of discontinuing propofol administration.

Revised (Discussion and Conclusions):

The evidence of increased glucose uptake by 18F-FDG PET and mitochondrial damage by electron microscopic investigation was not repeatedly evaluated during the time-course but a single time-point (18F-FDG PET on day 67 and endomyocardial biopsy 75), which is a potential limitation. Since the mitochondrial damage was detected 2 month later after PRIS onset, sustained mitochondrial damage may be a therapeutic target beyond the initial therapy of discontinuing propofol administration.

Minor concerns

1. Did the authors observe any changes in the blood glucose level or glucose tolerance of the patient?

Response:

According to the comment, we added the sentences.

Added (Case presentation):

Detailed examination including cardiac 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) was conducted to evaluate whether these late-phase cardiac events were related to PRIS. Cardiac 18F-FDG PET on day 67 demonstrated heterogeneous 18F-FDG uptake in the left ventricle with the maximum standardized uptake value (SUV) of 3.97. Blood glucose level before and after imaging was 90 mg/dL.

Added:

We observed no significant changes in the blood glucose and glucose tolerance of the patient during his hospital stay.

2. The authors may consider further quantification of mitochondrial degeneration in their tissue sample using markers for autophagy and apoptosis, e.g., BNIP3, FOXO3a, BCL-2, or OPA1.

Response:

Thank you for the comment. Unfortunately, we have no tissue sample available for further measurements.

Competing Interests: No competing interests were disclosed.

Reviewer Report 12 November 2020

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Susanne Haen

Institute of pathology and neuropathology, University of Tuebingen, Tuebingen, Germany

Petra Fallier-Becker

Institute of Pathology and Neuropathology, University Hospital of Tuebingen, Tuebingen, Germany

The concentration of several short-chain acylcarnitines in the patient's blood is missing.

Furthermore, the authors showed an electron microscopical image of mitochondria in the heart muscle with "myelinization of the cristae" but they don't write anything about the pathological background, the interpretation is missing. In our article (Vollmer *et al.*) the amorphous figures associated with mitochondria in the heart muscle could be interpreted as free fatty acids but they look completely different than the myelinated structures in the mitochondria in the article of Karasawa *et al.*

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

No

Is the case presented with sufficient detail to be useful for other practitioners?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pathology, Neuroscience, Electron Microscopy

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 16 Dec 2021

Satoshi Karasawa, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo, Japan

Thank you for taking your time to review and comment on our manuscript. Sorry for the delay in response due to COVID-19 pandemic. Unfortunately, we have no samples available to measure short-chain acylcarnitines. According to the comments, we added the sentences to improve the manuscript.

Added (Case presentation):

Electron microscopic investigation of the endomyocardial biopsy, which was taken on day 75 to examine the cause of cardiac dysfunction, revealed abnormal findings in the mitochondria of the cardiomyocytes, including myelinization of the cristae (Figure 2), which was interpreted as mitochondrial damage.

Previous (Discussion and Conclusions):

Mitochondrial damage was observed as a morphological finding in an electron microscopic evaluation of the heart in an autopsy case of PRIS⁵. Similarly, mitochondrial damage was observed in the endomyocardial biopsy two months after the onset in the present case.

Revised (Discussion and Conclusions):

Mitochondrial damage was observed as a morphological finding in an electron microscopic evaluation of the heart in an autopsy case of PRIS⁵. We found myelinization of the cristae in cardiomyocyte on day 75; however, similar findings were not observed in postmortem electron microscopical image of mitochondria of PRIS in the previous report⁵. Different

clinical course and timepoints may alter mitochondrial conditions. The autopsy study measured blood levels of short-chain acylcarnitines, while we have no blood sample available for the measurement. Further studies measuring blood levels of short-chain acylcarnitines would strengthen the case results.

Competing Interests: No competing interests were disclosed.

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