International Journal of Cardiology xxx (xxxx) xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Short communication

Reversible increase in stress-associated neurobiological activity in the acute phase of Takotsubo syndrome; a brain ^{18}F-FDG-PET study

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ARTICLE INFO

Keywords:
Takotsubo syndrome
Positron emission tomography
Amygdala
Stress
Brain–heart axis

ABSTRACT

Introduction: Takotsubo syndrome (TTS) is triggered mostly by physical and/or emotional stress that is processed in stress-associated brain regions, including the amygdala. However, it remains unclear whether such stress-induced brain activity is associated with TTS onset.

Methods and results: We acquired brain [^{18}F]-2-fluoro-deoxy-D-glucose (^{18}F-FDG) positron emission tomography in 4 TTS patients (44–82 yrs., 3 women) on days 2–4 (acute phase) and days 29–40 (recovery phase) after diagnosis of TTS was made by coronary angiography and left ventriculogram. The ^{18}F-FDG uptake was measured globally and also in the pre-defined regions of interest of the bilateral amygdala on the common Montreal Neurological Institute space; all ^{18}F-FDG images were normalized using automated image pre-processing. Amygdalar activity was calculated by dividing the ^{18}F-FDG uptake of the amygdala by the global brain uptake. Left ventriculograms showed that apical ballooning was typical at diagnosis and was then relieved in the recovery phase. Amygdalar activity in the acute phase (0.872 ± 0.032) was higher than in the recovery phase (0.805 ± 0.037) ($P = 0.013$).

Conclusions: We report here 4 cases of TTS showing higher amygdalar activity in the acute phase as compared with the recovery phase, suggesting that increased stress-induced neurobiological activity is associated with TTS onset.

1. Introduction

Takotsubo syndrome (TTS), also known as stress cardiomyopathy, is characterised by reversible cardiac wall-motion abnormalities without accompanying coronary artery disease [1]. In most cases, TTS is triggered by physical and/or mental stress [1], which is processed in stress-associated brain regions, including the amygdala [2]. Abnormalities of the stress-associated brain regions, such as neurological diseases (e.g., cerebral stroke [3], multiple sclerosis [4,5]) and alterations in neural activity [6–8], have been suggested to play a central role in TTS pathogenesis. Radfar et al. showed that amygdalar activity (AmyA) was higher in patients who developed subsequent TTS than in those who did not, using brain ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) [7]. Among patients who developed TTS, those with more AmyA developed TTS earlier compared to those with less AmyA [7]. Other reports showed that atrophy of the amygdala and its weakened neuronal connectivities with other stress/autonomic brain regions were noted even one year after TTS onset [9–11]. Although these neuroimaging findings indicate that amygdalar abnormality is associated with TTS pathogenesis, it remains unclear whether AmyA is abnormal also in the acute phase of TTS (within a week after the onset). Based on the previous study [7], we tested whether AmyA was higher in the acute phase of TTS compared with the recovery phase.

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https://doi.org/10.1016/j.ijcard.2021.09.057
Received 10 September 2021; Received in revised form 27 September 2021; Accepted 28 September 2021
Available online 4 October 2021

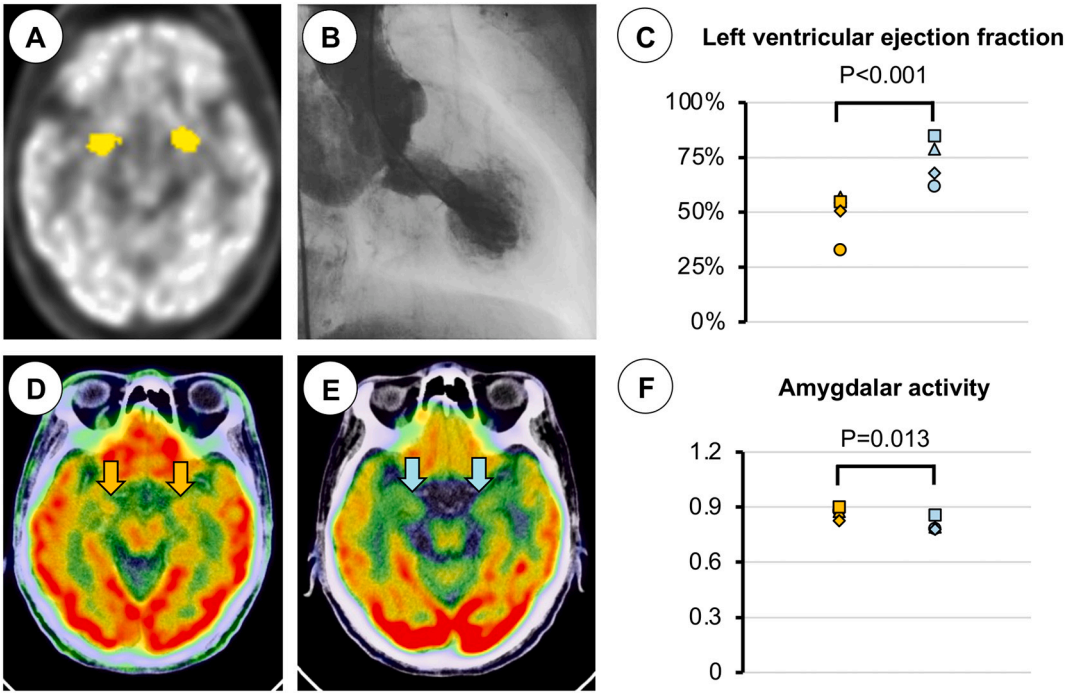

Fig. 1. Pre-defined regions of interest of the bilateral amygdala (yellow regions, **A**). A representative picture of left ventriculogram at enrollment (**B**). Left ventricular ejection fractions in the acute (orange shapes) and chronic phases (light-blue shapes) ($N = 4$, **C**). Representative pictures of brain ^{18}F-FDG-PET images on day 2 (**D**) and day 30 (**E**), where orange and light-blue arrows indicate the amygdala. Amygdalar activities in the acute (orange shapes) and chronic phases (light-blue shapes) ($N = 4$, **F**). The same shapes (circles, triangles, rectangles or rhombuses) corresponds to the left ventricular ejection fractions and amygdalar activities of the same patient (**C,F**). The pair-wise *t*-test was applied at a significance threshold of $P < 0.05$. Abbreviation: ^{18}F-FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2. Methods

We enrolled 4 patients (44–82 yrs., 3 women) in whom left ventriculogram showed left ventricular (LV) wall-motion abnormalities that did not have obstructive coronary lesions and extended beyond the territory of a single epicardial coronary artery on angiography. Each patient was later diagnosed as having TTS, based on reversible wall-motion asynergies on echocardiography on days 0–2 (acute phase) and days 25–47 (recovery phase) after the left ventriculogram. Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the ethical committee of Tohoku University Graduate School of Medicine (#2013–1-217, #2021–1-466).

Brain ^{18}F-FDG-PET images were acquired using a PET/CT scanner (Biograph 40 TruePoint, Siemens) on days 2–4 (acute phase) and days 29–40 (recovery phase) after the left ventriculogram. AmyA in the acute phase was compared with that in the recovery phase by the following steps with automated image pre-processing. First, all the ^{18}F-FDG-PET images were normalized to the standard Montreal Neurological Institute space using the free software SPM12 toolbox in Matlab [12]. Second, ^{18}F-FDG uptake was measured globally and was also in the pre-defined regions of interest of the bilateral amygdala (Fig. 1A, yellow regions) according to the Wake Forest University PickAtlas toolbox [13,14]. Third, AmyA was calculated by dividing the ^{18}F-FDG uptake in the amygdala by the global brain uptake in each image to minimize inter-image variability (conventional proportional scaling [15]). AmyA and LV ejection fractions were expressed as mean ± standard deviation and were compared between the acute and chronic phases using the pair-wise *t*-test. A statistical significance was set at $P < 0.05$.

3. Results

Characteristics of the 4 TTS patients included were shown in **Supplementary table 1**. A representative picture of a left ventriculogram is shown in Fig. 1B, where typical apical ballooning is noted. LV contraction was normalized from ejection fractions of 48.9 ± 10.9% in the acute phase to those of 73.5 ± 10.3% in the chronic phase (Fig. 1C, $P < 0.001$).

The brain ^{18}F-FDG-PET images, acquired after the left ventriculogram, showed that ^{18}F-FDG uptake in the amygdala in the acute phase (Fig. 1D, red arrows) seemed to be higher than that in the recovery phase (Fig. 1E, blue arrows). This was supported by the overall analysis of 4 patients; AmyA in the acute phase (0.872 ± 0.032) was higher than that in the recovery phase (0.805 ± 0.037) (Fig. 1F, $P = 0.013$). **Supplementary fig. 1** shows brain ^{18}F-FDG-PET images from the remaining 3 patients.

4. Discussion

In support of our hypothesis, and consistent with the previous finding [7], AmyA was higher in the acute phase (days 2–4) compared with the recovery phase (days 29–40) in the same TTS patients. The amygdala has numerous downstream targets that modulate autonomic and neuroendocrine stress responses [2]. A study of 41 patients who subsequently developed TTS showed that higher AmyA (≥ mean + 1SD) is associated with ~2-year earlier development of TTS, as compared to patients with lower AmyA [7]. In addition to this pre-onset finding, our results on the acute phase of TTS support the notion that abnormally increased AmyA causes TTS onset. In contrast, amygdalar volume and its connectivities with other stress/autonomic brain regions are reduced about one year after TTS onset [9–11]. Although further studies are needed to test the significance of these findings, it is possible that the amygdala is activated before TTS onset and during the acute phase but inactivated in the chronic phase (Fig. 2).

The first strength of this report is that we acquired brain ^{18}F-FDG-PET images within few days after TTS onset, since an image finding of

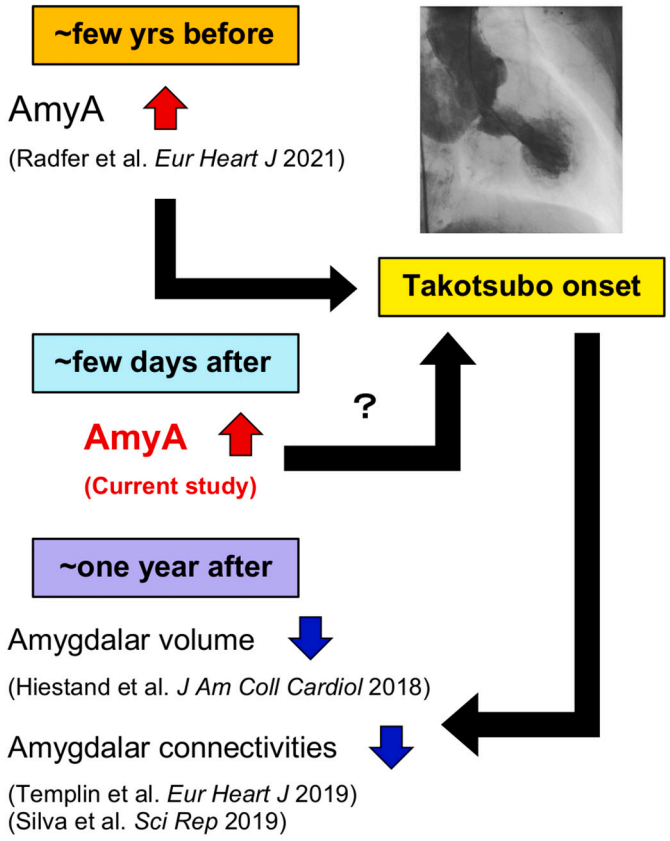

Fig. 2. Temporal changes in AmyA during the course of TTS. Abbreviation: AmyA, amygdalar activity.

TTS might disappear in the recovery phase; cardiac magnetic resonance shows late gadolinium enhancement in the area matched with wall-motion abnormality within a week after the onset [16], but this finding disappears 1–6 months later [16,17]. The second strength is that, by calculating AmyA using automated image pre-processing, inter-observer variability from manual assessment was avoided. However, this study is limited because it is a single-centre study with a small sample size and no control group. Thus, future multi-centre studies with larger sample sizes and control groups (e.g., cerebral FDG uptake in the acute and chronic phases of acute myocardial infarction) are needed to confirm the present findings.

5. Conclusion

The present analysis of brain ^{18}F-FDG-PET images in 4 cases of TTS showed higher amygdalar activity in the acute phase than in the recovery phase, which suggests that stress-associated neurobiological activation is associated with TTS onset.

Funding

This work was supported by the Grants-in-Aid program from the Japan Society for the Promotion of Science (20K07776).

Declaration of Competing Interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.09.057.

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