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Letters

RESEARCH LETTER

Neurometabolic Features of Takotsubo Syndrome

A Brain ^{18}F-FDG PET Case Control-Prospective Study

Takotsubo syndrome (TTS) is an acute heart failure syndrome featured by transient left ventricular systolic dysfunction. TTS pathophysiology is still unclear.[1] A retrospective analysis using brain ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomographic (PET)-computed tomography (CT) showed higher amygdala activity in subjects who subsequently developed TTS, suggesting a premorbid state.[2] The aim of this study was to evaluate potential features of brain metabolism in TTS patients compared with a control group.

Twenty consecutive TTS patients were enrolled at the University Hospital of Foggia, Italy, from the GEIST (German Italian Spanish Takotsubo; NCT04361994) registry according to the Heart Failure European Association criteria. Twenty control subjects matched for age and sex were included.

Data were acquired between October 2021 and January 2023. The median time between TTS event and acquisition of the ^{18}F-FDG PET/CT scans was 35 ± 20 months. Approval of the local ethics committee was obtained (No. 23/CE/30) and the study was conducted in accordance to the Declaration of Helsinki.

TTS patients underwent a neurological evaluation and administration of questionnaires such as the MOCA (Mini Mental State Examination and Montreal Cognitive Assessment). Brain ^{18}F-FDG PET/CT was performed according to the European Nuclear Medicine guidelines[3] using a General Electric Discovery 710 128 SL. Images were processed for voxel-based analysis using the Statistical Parametric Mapping software (London, United Kingdom, SPM version 12) running in Matlab 2023b (Mathworks Inc). Standardized uptake value ratio (SUVR) images were obtained by normalizing the uptake value of the whole brain with the average uptake value of the whole cerebellum. Amygdala activity was derived by averaging the mean standardized uptake values of the right and left amygdalae and dividing that value by the with the average uptake value of the whole cerebellum standardized uptake value and for additional analysis was divided the with the average uptake value of the prefrontal cortex (PFC).

Continuous variables were reported as mean ± SD and categorical variables as proportions. Groups were compared with unpaired Student's *t*-test or chi-square test as required. Repeated measures were analyzed with analysis of variance test. $P < 0.05$ was set as the threshold for significance.

The mean age was 71 ± 10 and 67 ± 7 years in the TTS and control group ($P = 0.15$). There was no group difference in terms of sex, cardiovascular risk factor, and drug therapy. TTS patients had lower Mini Mental State Examination and MOCA scores when compared to the control group (25.1 ± 4.7 vs 28.9 ± 0.9 and 23.9 ± 5.8 vs 28.8 ± 1.1, respectively; $P < 0.01$).

Neurological status was normal in 12 of 20 (60%) TTS patients and mild cognitive impairment was diagnosed in 8 of 20 (40%) TTS patients.

Patients with TTS showed higher amygdala activity as compared to the control group (0.95 ± 0.04 vs 0.88 ± 0.05; $P < 0.01$) (**Figure 1A**). Subanalysis after removing TTS patients with mild cognitive impairment yielded similar results (0.94 ± 0.04 vs 0.88 ± 0.05; $P < 0.01$).

SUVR voxel-wise whole brain analysis revealed, beyond the amygdala, several areas with significantly higher ^{18}F-FDG uptake in TTS patients vs controls including hippocampus, parahippocampal gyrus, temporal gyrus, and midbrain (**Figure 1B**) ($P < 0.025$). Moreover, this analysis revealed a significant reduction in ^{18}F-FDG uptake among TTS patients as compared with controls including frontal, parietal, and occipital cortices and thalamus. Subanalysis after TTS removing patients with mild cognitive impairment yielded similar results.

According to brain ^{18}F-FDG PET/CT timing following TTS episode (<1 year, 1-3 years, >3 years), patients were divided into 3 groups of 7, 6, and 7 patients, respectively. No difference in term of amygdala/PFC activity was found between groups with different timing of examination (0.71 ± 0.04 vs. 0.68 ± 0.09 vs 0.71 ± 0.05; $P = 0.49$). At multivariable analysis including age, sex, diabetes, hypertension,

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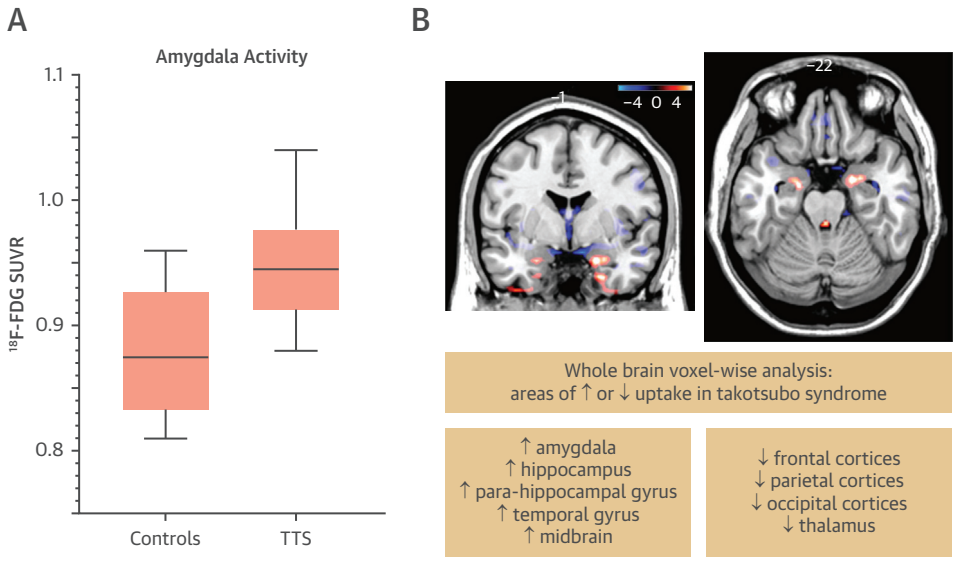
FIGURE 1 Neurometabolic Features of Takotsubo Syndrome Through ^{18}F-FDG Brain PET Evaluation



(A) Increased ^{18}F-FDG standardized uptake value ratio (SUVR) of amygdala in patients with takotsubo syndrome (TTS) as compared with matched control subjects ($P < 0.01$). (B) Whole brain voxel-wise analysis of ^{18}F-FDG uptake between TTS patients and controls. Red and blue areas highlight increased brain areas of uptake for TTS patients (red) and control group (blue).

MOCA score, and TTS, only TTS (b = 0.12 ± 0.03; $P = 0.01$) was significantly associated with amygdala/PFC activity.

We report a distinct brain metabolism among patients who experienced TTS. The main findings of the study are as follows: 1) higher amygdala activity (SUVR) can be found in TTS patients when compared with the control group; 2) at SUVR voxel-wise analysis, TTS patients had increased activity of the amygdala, hippocampus, parahippocampal gyrus, temporal gyrus, and midbrain; and 3) no difference in amygdala activity was found over the time following TTS episode.

The present study is the first to evaluate the long-term amygdala activity after a TTS episode. Increased right amygdala activity has been previously found in the hyperacute TTS phase.[4] In the present study, we found that higher activity of the amygdala in TTS patients also persisted over time. We hypothesize that TTS patients may be characterized by a chronic activation of the amygdala. During the acute phase of TTS, there are increased levels of anti-inflammatory interleukins, an indirect sign of a chronic inflammation.[5]

We found that TTS patients have higher uptake not only in the amygdala but also in the hippocampus, parahippocampal gyrus, temporal gyrus, and midbrain. Patients with TTS have a distinct brain metabolism featured by increased activity of those brain areas involved in emotional circuits. Tailored psychological support could be integrated into long-term TTS management.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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