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Screening for Pheochromocytoma in a Cohort of Patients with Takotsubo Cardiomyopathy: New insights on Prevalence and Screening Tests Reliability Surrounding the Acute Cardiac Event

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Background: According to Takotsubo cardiomyopathy (TCM) diagnostic criteria, pheochromocytoma and paraganglioma (PPGL) should be excluded as secondary causes. However, it is unclear whether PPGL screening in the setting of acute TCM is reliable. We aimed to assess the prevalence of PPGL and the reliability of PPGL screening in a cohort of patients with TCM. **Method:** We retrospectively reviewed data from patients admitted in a tertiary hospital between August 2012 and January 2021 with a diagnosis of TCM proven by typical echocardiography findings and no acute occlusion on coronarography, who were screened for PPGL by plasma metanephrines/normetanephrines (M/NM). If the first screening was positive, a second plasma M/NM sample was used for confirmation. Time between TCM diagnosis and PPGL screening was collected. **Results:** Among 64 patients identified with TCM, 42 underwent plasma M/NM screening. 81.0% were female, and the mean age was 67.4 ± 9.9 years old. Ten patients (23.8%) had a positive result. Of those, 8 patients had a weakly positive result (1-2×upper limit of normal [ULN]) and 2 had a strongly positive result (>2×ULN). Of those 10 patients, 6 underwent a second screening: 5 had a normal result and 1 had a weakly positive result (plasma NM 1.06×ULN). This patient underwent a third screening that was negative. In addition, an abdominal CT showed normal adrenal glands, and their chromogranin A levels were normal. Four patients had a positive initial PPGL screening, but they did not undergo a second screening: 3 died of causes unrelated to TCM before a second plasma M/NM sample was taken and one patient was lost to follow-up (his plasma NM was weakly positive at

1.29×ULN). They all had an abdominal CT that showed normal adrenal glands. Average time between TCM diagnosis and PPGL screening in all patients and in patients with a positive initial screening was 4.57 ± 3.91 and 3.38 ± 2.12 days, respectively. A linear regression model suggested an inverse relationship between plasma M/NM and time between TCM diagnosis and screening, with $R^2 = 0.2275$. **Conclusion:** TCM occurring as the initial presentation of PPGL is rare. All patients with a positive screening ended up being false positives in our study. The ratio of false positive results when screening for PPGL in the setting of acute TCM seems to be higher than in the general population, which could be explained by a hyperadrenergic state. It is unclear whether a shorter delay between TCM diagnosis and PPGL screening may be associated with more false positives. More research is needed to determine what is the optimal timing for PPGL screening in acute TCM and if higher cut-offs should be used to minimize false positive results.

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