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Prospective investigation of patent foramen ovale as a mechanism for brain metastasis in patients without prior lung involvement.

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Abstract

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Background: Brain metastases can lead to significant morbidity and mortality in patients with advanced cancer. Preventing metastatic disease to the brain could thus substantially improve outcomes. The mechanism of brain metastasis is incompletely understood. Circulating tumor cells drain to the right heart and through the pulmonary circulation, where they may manifest as lung metastases, and can circulate further to the left heart and then to the brain. However, in patients who develop brain metastases without prior lung involvement, metastatic cells may take an alternate route. We hypothesized that cancer cells may pass directly from the right to left heart via a patent foramen ovale (PFO), akin to paradoxical embolism. The prevalence of PFO is approximately 20-30% in the general population; if further elevated in this population, PFO may play a role in brain metastasis development, and ultimately, prophylactic PFO closure may provide benefit. We conducted a pilot study to investigate whether PFO is associated with brain metastases in patients without prior lung involvement. **Methods:** We prospectively identified patients with brain metastases from a non-lung primary cancer with no preceding lung metastases. Participants underwent a transcranial Doppler study to assess for PFO. Agitated saline was injected intravenously at rest and with Valsalva maneuver. High intensity signals were counted in the middle cerebral arteries for 1 minute after each injection. Spencer grade ≥ 3 indicated a positive study, consistent with the presence of PFO. **Results:** We accrued 9 participants who met inclusion criteria. Primary cancers were breast (6 participants), upper gastrointestinal (2 participants), and thyroid (1 participant). A positive study was identified in 2/9 (22.2%) participants. One individual was a female with breast cancer who had no preceding extracranial metastases, and the other individual was a male with duodenal adenocarcinoma whose only prior metastatic disease was distant lymphadenopathy, not active at brain metastasis diagnosis. No participants have developed lung metastases as of their most recent imaging. **Conclusions:** In this prospective pilot study, we found no increased prevalence of PFO in patients who develop brain metastases without preceding lung involvement compared to estimates for the general population. Though a larger study is needed, the development of brain metastases in these patients may reflect tumors' biological factors directing metastasis organotropism, rather than a structural pathway.