**Differential Effect of White-Matter Lesions and Covert Brain Infarcts on the Risk of Ischemic Stroke and Intracerebral Hemorrhage**

In this article, Kaffashian and colleagues sought to determine whether white matter hyperintensities and covert brain infarcts (BI) were associated with different stroke subtypes other than small vessel disease, as has been previously shown. To that end, they prospectively followed 1731 stroke-free participants from the Three-City Dijon Study who had brain magnetic resonance imaging data, for ≤12 years. An automated imaging processing software was used to detect, localize, and measure white matter hyperintensity volume (WMHV). Lesions ≥3 mm with the same signal as cerebrospinal fluid were considered covert BI. In this substudy, the majority of subjects were women (61%), and the mean age was 72±4 years. Mean follow-up was 9.6±2.4 years. All participants had some degree of WMHV, and 9% had >1 covert BI. Total high and periventricular WMHV and extensive periventricular WMHV were associated with ischemic and hemorrhagic strokes, especially hemorrhagic strokes. Of the ischemic stroke subtypes, cardioembolic stroke was associated with extensive periventricular WMHV. Conversely, deep WMHV and extensive WMHV were associated with hemorrhagic strokes only. Interestingly, covert BI was associated with incident cerebral hemorrhage but not with incident ischemic stroke. Furthermore, lacunes were associated with both stroke types, but the association was much more robust for incident intracerebral hemorrhage than for incident ischemic stroke. As expected, lacunes were associated with small vessel ischemic stroke. This study’s surprising findings may raise certain considerations regarding the management of patients with covert BI and extensive WMHV, as discussed by the authors. Namely, should antithrombotics be given to patients with covert BI, or could that increase their risk of cerebral hemorrhage? Should atrial fibrillation be sought for in patients with extensive periventricular WMHV? These observations deserve attention, but need to be confirmed in other large prospective studies. See p 1923.

**Clinical Outcomes of Transplanted Modified Bone Marrow–Derived Mesenchymal Stem Cells in Stroke: A Phase 1/2a Study**

There is a paucity of effective treatments for chronic stroke survivors, which might lead to improved functional outcomes. Therefore, cell-based therapies are being explored in multiple studies as potential routes for neurorestoration. Many studies have shown safety of such cell-based therapies, and it is possible that the intracerebral route has the largest clinical benefit. Preclinical studies of stereotactic cerebral implantation of modified bone marrow–derived mesenchymal stem cells transiently transfected with the human Notch-1 intracellular domain (SB623 cells) have showed improvements in locomotor and neurological function, and a reduction in peri-infarct cell loss. Thus, in an open-label, single-arm study, Steinberg and colleagues sought to evaluate the safety and clinical efficacy of placement of SB623 cells at the margin of nonhemorrhagic strokes in patients who had chronic stable motor deficits, 6 to 60 months after their stroke. They enrolled 18 patients in 2 American sites. Patients’ mean age was 61 years, and 61% were women. The primary outcome was the European Stroke Scale (ESS) at 6 months, and other functional scales were also performed. Patients were divided into 3 cohorts receiving different dosages of SB623 cells. The cells were implanted by magnetic resonance imaging–guided stereotactic technique. The baseline stroke volume was 42 cc. All patients experienced at least 1 treatment emergent adverse event, of which the most common were headaches, nausea, vomiting, depression, muscle spasticity, and fatigue. Four treatment emergent adverse events were possibly related to the procedure (spasticity, gait disturbance, and procedural headache). Six serious treatment emergent adverse events were reported, and only 1 felt to be related to the procedure (subdural collection). Clinical outcome data, available in 16 patients, showed significant improvement in the ESS at 6 and 12 months and in the National Institutes of Health Stroke Scale score and the Fugl-Meyer score at 12 months. New signal changes were noted on fluid-attenuated inversion recovery magnetic resonance imaging, and these correlated significantly with favorable changes in neurological recovery scales at 12 months. Therefore, in this study stereotactic implantation of SB623 cells was generally safe and well tolerated, and led to significant functional improvement at 12 months. Further studies are needed to confirm these findings, and we also await the results of 24-month outcomes in this patient population. See p 1817.

**Postmenopausal Hormone Therapy and Risk of Stroke: Impact of the Route of Estrogen Administration and Type of Progestogen**

There are currently many concerns about the use of postmenopausal hormone therapy, given its potential risks for thromboembolism and stroke, as demonstrated by the Women’s Health Initiative (WHI) study. In the WHI, patients received oral hormone therapy with or without a progestogen, depending on the presence of an intact uterus. Interestingly, there are data that show that oral but not transdermal estrogens activate blood coagulation and increase risk of thromboembolism; and that the type of progestogen might also determine risk of thrombosis. To further clarify this issue, Canonico and colleagues conducted an elegant nested case–control study to investigate the role of estrogens according to the route of administration, as well as the role of progestogens in ischemic stroke. To that end, they used the French National Health Insurance database. They sought data on all women aged 51 to 62 years from 2009 to 2011 (n=5532341), and they matched each hospitalized ischemic stroke (n=3144) case with age, location-matched controls (n=12158). Ischemic stroke risk was increased for oral estrogens (OR, 1.58; 95% CI, 1.01–2.49) in a dose-dependent fashion, but not for transdermal estrogens (OR, 0.83; 95% CI, 0.56–1.24). Interestingly, age did not affect the association of estrogens with risk of ischemic stroke. Furthermore, stroke risk varied according to the type of progestogen: progestosterone, progesterone derivatives, and nortestosterone derivatives were not associated with stroke, but the use of nonpregnane derivatives led to higher ischemic stroke risk (OR, 2.25; 95% CI, 1.05–4.81). The authors concluded that transdermal estrogens alone or combined with micronized progesterone might be the safest option to alleviate climacteric symptoms, while at the same time minimizing the risk of stroke and thromboembolism. These important observations merit replication in clinical trials to definitively determine the safety of hormone therapy. See p 1734.
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