Benefits of PFO Closure Confirmed in Newly Published Trial Data

Data from three different studies recently published in *The New England Journal of Medicine* show that closing a patent foramen ovale (PFO) significantly reduces the rate of recurrent stroke compared with medical therapy in patients who experienced a cryptogenic stroke and had a PFO.

In the RESPECT study, the Amplatzer PFO Occluder (St. Jude Medical/Abbott Laboratories) was associated with a 45% reduction in the risk of ischemic stroke and a 62% reduction in the rate of cryptogenic stroke (*NEJM*; 377:1022-1032). It was also associated with a strong safety profile, with a low risk of device- or procedure-related complications and no increased risk of adverse events, such as atrial fibrillation.

The REDUCE trial showed that patients undergoing PFO closure with Cardioform Septal Occluders (WL Gore and Associates) plus antiplatelet therapy experienced a significantly lower incidence of new brain infarctions as compared to patients receiving antiplatelet therapy only (1.4% vs 5.4%, respectively) at 3.2-year follow-up (*NEJM*; 377:1033-1042). The incidence of silent brain infarction did not differ significantly between the study groups. Additionally, the authors noted that PFO closure was associated with higher rates of device complications and atrial fibrillation.

Finally, in the CLOSE trial, which evaluated PFO closure in patients who had had a recent cryptogenic stroke attributed to PFO with an associated atrial septal aneurysm or large interatrial shunt, investigators found that no strokes occurred in the PFO closure group more than five years after PFO closure, whereas stroke occurred in 14 patients in the antiplatelet-only group (*NEJM*; 377:1011-1021). Procedural complications were observed in 5.9% of patients in the PFO closure group, which also had a higher rate of atrial fibrillation (4.6%) than the antiplatelet-only group.

Cognitive Decline in Healthy Older Adults Tied to Greater Tau Burden

Cognitive decline in clinically healthy older adults has been linked with greater tau burden in the entorhinal cortex, in a new study published in *JAMA Neurology* (E-pub October 2). The study included 133 clinically healthy participants with a mean age of 76 years who underwent cross-sectional florbetapir F 18 positron emission tomography imaging for tau and Pittsburgh compound B carbon 11–labeled PET imaging for β-amyloid (Aβ). The investigators measured subjective cognitive decline (SCD) by using a previously published method of z-transforming subscales from the Memory Functioning Questionnaire, the Everyday Cognition Battery Memory Test, and a questionnaire.

Results show that 29.3% of participants exhibited a high Aβ burden, while greater subjective cognitive decline (SCD) was associated with increasing entorhinal cortical tau burden and Aβ burden, but not inferior temporal tau burden. Additionally, the association between entorhinal cortical tau burden and SCD was largely unchanged after accounting for Aβ burden, and no interaction influenced SCD. These results were reinforced in an exploratory post hoc whole-brain analysis indicating that SCD was predominantly associated with greater tau burden in the entorhinal cortex. The authors conclude that subjective cognitive decline indicates accumulation of early tauopathy in the entorhinal cortex, and to a lesser extent, elevated global levels of Aβ.

“Our findings suggest multiple underlying pathways that motivate SCD that do not necessarily interact to influence SCD endorsement. As such, multiple biological factors must be considered when assessing SCD in clinically healthy older adults,” they write.

Remotely Supervised Transcranial Stimulation Shown to Reduce Fatigue in Patients with MS

New findings published in the *Multiple Sclerosis Journal* (E-pub September 22) suggest that transcranial direct current stimulation (tDCS) is a promising option for reducing fatigue in patients with multiple sclerosis (MS). Researchers at NYU Langone Health developed a telerehabilitation protocol that delivers tDCS to participants at home using specially designed equipment and real-time supervision. They administered remotely supervised tDCS paired with 20 minutes of cognitive training in two studies, assessing fatigue using the Patient-Reported Outcomes Measurement Information System (PROMIS)—Fatigue Short Form. The
first study delivered 10 open-label tDCS treatments compared to a cognitive training-only condition, showing modest fatigue reduction in the active group. The second study was a randomized trial of active or sham delivered for 20 sessions that showed a statistically significant reduction for the active group. Although the findings point to a future role for iDCS technology in treating fatigue, the researchers emphasize the need to validate the findings in larger studies. They also strongly caution individuals with MS not to try over-the-counter stimulation technologies at home or outside of a rigorous research setting.

Seventeen New Genes Linked to Parkinson’s Disease

A new study has discovered 17 novel genetic variants associated with Parkinson’s disease, several of which are considered targets for intervention. Published in Nature Genetics (E-pub September 11), the genome-wide association study represents a collaboration between Genentech and the personal genomics company 23andMe. Investigators compared 6,476 PD cases with 302,042 controls as well as a meta-analysis of over 13,000 PF cases, 95,000 controls, and 9,830 overlapping variants. Using a neurocentric strategy to assign candidate risk genes in 35 loci, investigators identified 17 novel risk loci. Of note, a significant number of variants were related to lysosomal and autophagy pathways, which are important for clearing out protein aggregates and dysfunctional components of the cell. Other variants included genes related to mitochondria, neuronal survival, and immune cell function. Genentech and 23andMe plan to continue their collaboration to accelerate research in PD and translate genetic discoveries into prospective drug discovery targets.

Progression-Free Survival Outcome Measures Effective for Evaluating Huntington’s Disease Progression

Progression-free survival (PFS) outcomes may offer insight into the progression of Huntington’s disease and could guide future research, new findings suggest (JAMA Neurology, E-pub September 18). Researchers evaluated data from the two-phase, longitudinal cohort study called Track and from a longitudinal cohort study called the Cooperative Huntington Observational Research Trial (COHORT). After adjusting for initial progression, they found that PFS curves of the Track mutation carriers showed good external validity with the COHORT mutation carriers. “For required sample size, PFS with a motor diagnosis or total motor score progression required about four times fewer participants than a motor diagnosis alone. Including additional cognitive progression events further reduced the number,” the authors write. They conclude that reasonably sized prediagnosis Huntington’s disease trials can be planned with progression-free survival.

More Headlines from NeurologyWire

US Postal Service Issues Alzheimer’s Disease Semi-Postal Stamps

New stamps for Alzheimer’s disease awareness are coming soon from the US Postal Service. Under its semi-postal discretionary program, the Postal Service will issue five stamps over a 10-year period to advance causes it considers to be “in the national public interest and appropriate,” with each stamp to be sold for no more than two years. The Alzheimer’s semi-postal stamp will be issued during National Alzheimer’s Awareness Month, and net proceeds will be distributed to the US Department of Health and Human Services.

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Blood Test Shown to Accurately Identify Alzheimer’s Disease

A blood test may help identify and diagnose Alzheimer’s disease. In a study published in *Proceedings of the National Academy of Sciences of the United States of America* (E-pub September 4), researchers used attenuated total reflection FTIR spectroscopy combined with chemometric techniques to analyze blood plasma samples in 347 individuals with neurodegenerative disease. They identified Alzheimer’s disease with 70% sensitivity and specificity, which after the incorporation of ApoE 4 genotype increased to 86% when individuals carried one or two alleles of E4. Moreover, early Alzheimer’s cases were identified with 80% sensitivity and 74% specificity. The authors conclude that spectroscopy could provide a simple and robust diagnostic test, but that more work is needed to understand the extent to which the test can identify patients who have not yet developed symptoms and differentiate stages of severity.

Project ALS and Amylyx Team Up to Test ALS Compound

Project ALS and Amylyx Pharmaceuticals are collaborating to undertake pre-clinical studies to advance the understanding of Amylyx’s oral compound AMX0035 for the treatment of ALS. The studies will be conducted at the Project ALS Pre-Clinical Core at Columbia University’s Motor Neuron Center and will complement the company’s recently initiated Phase 2 clinical program of AMX0035 for the treatment of ALS. The Project ALS Pre-Clinical Core at the Columbia University’s Motor Neuron Center has established an integrated and standardized platform for the testing and validation of new therapeutic strategies in recognized experimental models of ALS and for biomarker discovery. The Core, developed in collaboration with Project ALS, will accelerate
the translation of new promising therapies to patients by facilitating speedy testing of new therapeutic leads discovered by laboratories studying motor neuron biology, genetics, and genomics. The collaboration is an outgrowth of previous studies by The Project ALS Pre-Clinical Core at Columbia University of tauroursodeoxycholic acid, one of the components of AMX0035.

Annual Short-Course Therapy with Investigational Oral Agent Effective in Relapsing MS

New results suggest that patients with relapsing MS treated with two annual short courses of investigational cladribine tablets (EMD Serono) may have similar clinical benefits to those seen with four years of treatment with the same medication. Published in the *Multiple Sclerosis Journal* (E-pub August 17), the data from the CLARITY Extension study assessed the annualized relapse rate and confirmed three-month EDSS progression among other efficacy endpoints in 806 patients with relapsing MS. The proportion of patients who remained relapse-free at the end of four years was similar to the patients who received cladribine tablets 3.5mg/kg in CLARITY followed by placebo in CLARITY Extension (75.6%) and those who received cladribine tablets 3.5mg/kg in both studies (81.2%). The proportion of patients who remained free of three-month EDSS progression was also similar between the treatment groups (72.4% vs. 77.4%). Adverse event rates were similar in patients who received cladribine tablets in CLARITY followed by placebo in CLARITY Extension, and those who received cladribine tablets in both studies.

In August 2017, the European Commission (EC) granted marketing authorization for cladribine tablets, marketed as Mavenclad in the European Union (EU), for the treatment of relapsing forms of multiple sclerosis in the 28 countries of the EU in addition to Norway, Liechtenstein, and Iceland. Merck KGaA plans additional filings for regulatory approval in other countries, including the US.