New Evidence Ties Low Vitamin D Levels to Neurological Diseases

Low levels of vitamin D have been associated with a variety of medical conditions in the last several years, including neurological conditions. More recently, the role of vitamin D in diseases such as Parkinson’s disease and multiple sclerosis has become the subject of increased inquiry.

**Multiple Sclerosis.** Although the association of low vitamin D levels and onset of MS has long been recognized, new findings offer the most compelling evidence yet that lack of vitamin D may, in fact, be a “causal susceptibility factor” for MS. In a Mendelian randomization study published in the August 25 edition of *PloS Medicine*, investigators identified single nucleotide polymorphisms (SNPs) associated with 25-hydroxyvitamin D (25OHD) level in 33,996 participants. Four SNPs were genome-wide significant for 25OHD level and all four SNPs lay in, or near, genes strongly implicated in separate mechanisms influencing 25OHD. The researchers then tested the extent to which the 25OHD-decreasing alleles explained variation in 25OHD level, finding that the count of 25OHD-decreasing alleles across these four SNPs was strongly associated with lower 25OHD level. Moreover, they found that each genetically determined one-standard-deviation decrease in log-transformed 25OHD level conferred a 2.0-fold increase in the odds of MS. This result persisted in sensitivity analyses excluding SNPs possibly influenced by population stratification or pleiotropy and including only SNPs involved in 25OHD synthesis or metabolism. Thus, although the link between insufficiency and MS is now clear, the authors concluded more investigation is required to understand whether vitamin D sufficiency can delay, or prevent, MS onset.

**Parkinson’s Disease.** Low vitamin D levels may also play a role in early Parkinson’s disease (PD), according to new findings evaluating the relationship between serum vitamin D levels and flow-mediated dilation (FMD), a widely used clinical marker of endothelial function. In a study published in the *Journal of Neural Transmission* (September 5, 2015), researchers found that mean vitamin D levels were significantly lower in the PD patients than in the controls (21.8 ± 9.5 vs. 25.2 ± 9.3 ng/mL). Additionally, FMD was significantly lower in the PD patients (7.1 ± 1.8 percent) than in the controls (8.1 ± 2.1 percent). The authors also noted that vitamin D was “significantly” associated with FMD independent of age, cardiovascular disease risk factors, body mass index, motor Unified PD Rating Scale status and homocysteine levels.

Florbetaben Found Accurate in Detecting Beta-Amyloid Plaques in Patients with Suspected Alzheimer’s Disease

New findings confirmed the accuracy and reliability of florbetaben in detecting beta-amyloid plaques in the brain of patients with suspected Alzheimer’s disease (AD). Published in the August issue of *Alzheimer’s & Dementia: The Journal of the Alzheimer’s Association*, the Phase III trial findings compared florbetaben to post-mortem pathology. According to the results, 46 of 47 neuritic beta amyloid-positive cases were read as Positron Emission Topography (PET) positive, and 24 of 27 neuritic beta amyloid plaque-negative cases were read as PET negative. The authors noted that the findings indicate that florbetaben PET shows high sensitivity and specificity for the detection of histopathology-confirmed neuritic beta amyloid plaques and may thus be a valuable adjunct to clinical diagnosis, especially for the exclusion of AD.

In March 2014, the FDA approved Neuraceq (florbetaben F18, Piramal Imaging) for PET imaging of the brain to estimate beta-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer’s disease (AD) and other causes of cognitive decline. It is one of three currently available diagnostic radiopharmaceuticals for this indication.
Amgen and Novartis Partner to Develop Alzheimer’s and Migraine Treatments

Amgen and Novartis have entered into global partnership to co-develop treatments for Alzheimer’s disease and migraine. Under the agreement, the companies will combine their individual BACE programs into a global co-commercialization and co-development arrangement, in which Novartis’ experimental BACE inhibitor CNP520 will be the lead compound.

Amgen will make upfront and milestone payments to Novartis, with Amgen holding responsibility for disproportionate R&D costs for an agreed-upon period followed by a 50/50 cost and profit share arrangement. Additionally, Novartis will acquire global co-development rights and commercial rights outside of the US, Canada, and Japan to Amgen’s migraine portfolio, including AMG 334, which is currently in late-stage development. Novartis will also hold responsibility for disproportionate global R&D expenses for an agreed-upon period on the migraine programs, while Amgen will additionally receive royalties on sales.

Key Contributors to the Vulnerability of Dopamine Neurons in Parkinson’s Disease Identified

Although it remains unclear why dopamine (DA) neurons are particularly vulnerable to cellular dysfunctions resulting in a loss of neurons in patients with Parkinson’s disease, new data indicate that the heightened vulnerability of nigral DA neurons in Parkinson’s disease may be directly due to their particular bioenergetic and morphological characteristics. In a new study published in Current Biology (August 27), investigators showed that vulnerable nigral DA neurons differ from less vulnerable DA neurons such as those of the VTA (ventral tegmental area) by having a higher basal rate of mitochondrial OXPHOS (oxidative phosphorylation), a smaller reserve capacity, a higher density of axonal mitochondria, an elevated level of basal oxidative stress, and a considerably more complex axonal arborization. They also demonstrated that reducing axonal arborization by acting on axon guidance pathways with Semaphorin 7A reduces in parallel the basal rate of mitochondrial OXPHOS and the vulnerability of nigral DA neurons to the neurotoxic agents MPP+ (1-methyl-4-phenylpyridinium) and rotenone. Blocking L-type calcium channels with isradipine was protective against MPP+ but not rotenone.

Class II HLA Interactions Shown to Modulate Genetic Risk for MS

A newly published study has identified specific interactions between human leukocyte antigen (HLA) genes that modulate risk of multiple sclerosis (MS). According to findings published in a recent edition of Nature, investigators built a high-resolution map of HLA genetic risk by analyzing high-density data on 17,465 cases and 30,385 controls from 11 cohorts of European ancestry, in combination with imputation of classical HLA alleles. They found evidence for two interactions involving pairs of class II alleles: HLA-DQA1*01:01–HLA-DRB1*15:01 and HLA-DQB1*03:01–HLA-DQB1*03:02. The authors observed that they found no evidence for interactions between classical HLA alleles and non-HLA risk-associated variants and estimate a minimal effect of polygenic epistasis in modulating major risk alleles.

Gene Mutation Identified in Severe Infant Epilepsy

Confirming the role of the protein KCC2 in human epilepsy, a new study has discovered a mechanism for severe infant epilepsy. Encoded by SLC12A5, KCC2 has been known to play a fundamental role in the synaptic inhibition associated with epilepsy. In a study recently published in Nature Communications (September 3), investigators showed recessive loss-of-function SLC12A5 mutations in patients with a severe infantile-onset pharmacoresistant epilepsy syndrome, epilepsy of infancy with migrating focal seizures (EIMFS). Decreased KCC2 surface expression, reduced protein glycosylation, and impaired chloride extrusion contribute to loss of KCC2 activity, the investigators noted, thereby impairing normal synaptic inhibition and promoting neuronal excitability in this early-onset epileptic encephalopathy.
Increased RNA in Common ALS Genetic Mutation a Key Factor in Development of Disease

Two new studies funded in part by the ALS Association (www.alsa.org) highlight new discoveries regarding the C9orf72 mutation, the most common genetic defect associated with amyotrophic lateral sclerosis (ALS). The studies, both published earlier this month in Nature, emphasize that a key driver of the development of ALS due to this mutation is an export-import imbalance between the cell’s nucleus and its non-nuclear portion, or cytoplasm.

In the first study, investigators analyzed fruit flies carrying various forms of the mutation. They discovered 18 genes that worked to either worsen or mitigate the effects of the mutation, all of which encoded either components of the nuclear pore or other proteins involved in regulating traffic of RNA and proteins in and out of the cell nucleus. Moreover, the investigators observed an increase in the amount of RNA retained in the nucleus, a change that was also seen in cells derived from people with disease due to the C9orf72 mutation.

The second study focused on the expanded RNA of the C9orf72 mutation, particularly how its interaction with a protein called RanGAP1 that appears to interrupt the normal regulation of cross-membrane flow of materials. Importantly, RanGAP1 controls traffic of materials across the membrane separating the nucleus from the cytoplasm in all cells, including the motor neurons affected in ALS. The investigators observed the defect in both a fly model and in cells from people with ALS. They concluded that the defect could be mitigated with treatments that targeted the extra RNA produced by the mutation.

Evidence of Disease Activity in MS a Possible Marker of Treatment Effect

RRMS patients who use more first line and less second line disease modifying treatment may be more like to show evidence of disease activity (EDA) compared to others with the disease, a new study suggests. (PLoS One, e-pub) In fact, at one year follow up, EDA patients show progression of disability, while those with no evidence of disease activity (NEDA) actually improved.

The present study measured disability, cognition, treatment and gray matter (GM) atrophy rates of patients with early RRMS patients at baseline and at one year follow-up. At one year, 46 percent of patients had EDA.

The patients groups had similar disability levels at baseline, but they differed in disability at follow-up. Cognitive function was stable in both patient groups. Subcortical GM atrophy rates were higher in EDA patients than healthy controls. The researchers say that these “results support the relevance of NEDA as outcome in RRMS and indicate that pathological neurodegeneration in RRMS mainly occur in patients with evidence of disease activity.”

No Good Evidence to Support OTC Antioxidants in MS

There is no clinical evidence to support recommendation of OTC antioxidant compounds for patients with MS, a new analysis shows (Mult Scler, epub) However, preclinical evidence is potentially promising for epigallocatechin-3-gallate (ECGC) and (alpha)-lipoic acid (ALA) in animal models.

Only 145 of 3,507 publications met inclusion criteria for the analysis. These included compounds such as ALA, antioxidant vitamins, Ginkgo biloba, quercetin, resveratrol, and ECGC. However, these studies were in animal models and demonstrated no or conflicting evidence for most OTC antioxidants. ECGC and ALA both consistently showed anti-inflmmatory/anti-oxidant effects and reduced neurological impairment in preclinical trials.
Neurology in the Media

Trailer for NFL Concussion Film Debuts

Columbia Pictures recently released the trailer for Concussion, a new film examining concussions in American football. Starring Will Smith and Alec Baldwin, the film chronicles forensic pathologist Bennet Omalu’s discovery of chronic traumatic encephalopathy (CTE) in football players’ brains. The movie is set for release this December.


Oliver Sacks Remembered

Following the death of Oliver Sacks in August, various media sources offered tribute to the famed neurologist’s life and career. Many accounts focused on Dr. Sacks’ work on individuals with unusual brain disorders, as well as his experimentation with recreational drugs.


“While I’ve always wanted to get people’s stories, I also like to know what’s going on in the brain, and how this wonderful two or three pounds of stuff in the head is able to underlie our imagination, underlie our soul, our individuality.”

—Oliver Sacks

Excerpted from Jon Hamilton’s remembrance for National Public Radio (link above)