WESTERN PACIFIC ALS-PARKINSONISM-DEMENTIA COMPLEX: GENETIC OR TOXIC ETIOLOGY? FAVORING A GENOTOXIC ETIOLOGY

Peter S. Spencer, Glen E. Kisby
Health & Science University, Portland, Oregon, USA and Department of Basic Medical Sciences, Western University of Health Sciences, College of Osteopathic Medicine of the Pacific Northwest, Lebanon, Oregon, USA

Discovery of the etiology and pathogenesis of the western Pacific amyotrophic lateral sclerosis and parkinsonism-dementia complex (ALS-PDC), a prototypical tauopathy, promises to illuminate understanding of related neurodegenerative disorders worldwide. High-incidence ALS-PDC is known among three island populations: Chamorros of Guam and Rota in the Marianas; Japanese residents of Kii Peninsula, Honshu; and Auyu/Jacqai linguistic groups in West Papua, New Guinea. A plausible etiologic factor for ALS-PDC, whether genetic, infectious, or toxic, must be common to all three affected populations. A genetic etiology is unlikely on four counts. First, Chamorros, Japanese and New Guineans are genetically distinct. Second, a highly penetrant genetic disorder is inconsistent with the declining disease prevalence in all three populations. Third, genetic mutations or polymorphisms linked to neurodegenerative diseases are not found in Kii or Guam patients. Fourth, ALS-PDC has not surfaced in offspring of Chamorros who migrated from Guam and bore children after moving to the continental USA.

An environmental etiology is probable for three reasons. First, declining ALS-PDC prevalence has accompanied post World War II development of Guam and Kii, and societal evolution in West Papua (from forest-gathering to planting of food), where cases have been most frequent in least-developed communities. Second, age of onset of patients with Kii and Guam ALS-PDC has increased and, best seen in the latter, the clinical presentation has evolved over 60-70 years from young-onset ALS, to PD in middle age and older, to dementia in the elderly. Third, ALS-PDC has affected occasional non- Chamorro migrants to Guam after prolonged residence (years/decades) on the island.

An infectious environmental agent is unlikely for three reasons. First, disease has not spread beyond the three ALS-PDC isolates. Second, the “incubation period” for Guam ALS-PDC is long (years/decades) and not proceeded by any recorded acute illness (unlike post-encephalitic parkinsonism). Third, unlike the transmissible neurodegenerative disease kuru, experiments to transmit ALS/PDC from human brain to primate failed.

A non-infectious environmental etiologic agent, while probable, is unlikely to be associated as proposed with poor mineralization of water or soil leading to a parathyroid-driven increased uptake of minerals and “bystander” metals (aluminum, manganese) with potential neurotoxicity.

First, disease prevalence has declined in West Papau without any change in water source. Second, domestic and other animals using the same source of water (West Papua, Guam, Kii) do not develop brain degeneration. Third, parathyroid function is unremarkable in (Guam) ALS-PDC. Fourth, motorsystem disease is lacking in laboratory animals placed on low mineral diets with concomitant exposure to metals.

An environmental agent of significance is likely to be a naturally occurring component common to all ALS-PDC foci. First, the West Papua focus evolved without outside contact. Second, all three population groups used neurotoxic plants for either medicine (West Papua, Kii) or medicine and food (Guam), but only one (medicinal use of raw cycad seed) is common to all three ALS-PDC foci. Third, epidemiology has linked Guam ALS-PDC to preference for traditional food.

Human contact with cycad neurotoxins in all three ALS-PDC foci is a plausible etiologic trigger for neurodegenerative disease. First, large animals grazing on cycads develop a progressive (but poorly characterized) neuromuscular disorder (neurocycadism) associated with long-tract degeneration.

Second, Guam patients attributed ALS (lytico) to excessive cycad exposure. Thirdly, childhood and young adult use of cycad-based food on Guam is linked with ALS-PDC. Fourth, ALS and prior medicinal use of raw cycad seed has been demonstrated in West Papua (subcutaneous exposure) and Kii (repeated oral exposure). Fifth, laboratory animals fed incompletely detoxified cycad flour developed neurological deficits.

Cycad neurotoxic substances include the principal component cycasin (which induces large-animal neurocyadism) and minor amino acids beta-N-methylamino-L-alanine (L-BMAA) and beta-Noxalylamino-L-alanine (L-BOAA). Content of residual cycasin (but not L-BMAA) in Chamorro cycad flour correlates with Guam ALS and PD incidence. Cycasin and L-BMAA are taken up by rodent brain tissue and metabolized to agents that damage DNA (genotoxins). Cycasin is metabolized to methylazoxymethanol (MAM), and MAM and L-BMAA to the genotoxin formaldehyde. MAM-induced DNA damage (O6-guanine methylation, O6-mG) disrupts rat brain development and, with postnatal exposure, causes ectopic multinucleated neurons in the rat cerebellum comparable to those found in the Guam and Kii ALS-PDC cerebellum. Because of low DNA repair levels (O6-mG methyltransferase, MGMT), O6-mG is poorly repaired in the young adult human brain, and MAM treatment of MGMTdeficient mice leads to persistent brain tissue DNA damage and the activation of cell signaling pathways linked to human neurological

disease. Repeated oral treatment of cynomolgus monkeys with large doses of L-BMAA induces a motorsystem disease with upper and lower-motor-neuron pathology, including intraneuronal structures resembling the twisted filaments of tau-rich neurofibrillary tangles. LBOAA is a potent glutamate (AMPA) agonist and excitotoxin responsible for the self-limiting upper motor neuron disease neurolathyrism; unlike L-BMAA, L-BOAA is not taken up by rat brain and does not produce genotoxic metabolites. Another cycad component, beta-sitosterol, is (like L-BOAA) an improbable cause of ALS-PDC given its long-time use in treatment of prostate hypertrophy.

In summary, early life exposure to cycad genotoxins (MAM + L-BMAA) may produce unrepaired

DNA damage in post-mitotic neurons that results in the persistent activation of cell signaling pathways that favor development of neuronal pathology [1-3], with the eventual appearance of young-onset ALS (heavy genotoxic dosage), middle-age onset of PD (intermediate dosage), dementia in the elderly (low dosage), or sub-clinical neurofibrillary pathology (lowest dosage).

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