Chapter 9

Lithium, Cognitive Decline and Alzheimer’s Disease

Another American develops Alzheimer’s disease every 69 seconds.
- Alzheimer’s Association

In 2011, the news media delivered stories about several famous Americans with Alzheimer’s disease. Country music singer Glen Campbell announced that he was diagnosed with Alzheimer’s, former Tennessee women’s basketball coach Pat Summitt was diagnosed with an early-onset form of the disease, and actor Peter Falk (1927-2011) passed away from cardiorespiratory arrest, with pneumonia and Alzheimer’s disease as underlying causes.

Campbell, who has been in show business for more than 50 years, had memory difficulties on-stage.

Glen Campbell (b. 1936), whose music helped move country into the mainstream in the 1970s, was diagnosed with Alzheimer’s in early 2011.
during his Goodbye Tour in 2012. His songs are so well known that his fans were able to cover for him by singing along. In Galvaston, the city that lent its name to one of his most famous songs, Glenn joked about his condition. He said, “What’s that song we’re gonna play out here?”

**Very Few People on Long-Term Lithium Develop Alzheimer’s**

In July 2004, Paula Nunes and colleagues from the University of São Paulo, Brazil, presented research at the 9th International Conference on Alzheimer’s Disease suggesting lithium provides a neuroprotective effect. In 74 elderly people with bipolar disorder, four percent of those taking lithium had Alzheimer’s disease, compared with 21% of patients who were not taking the drug (1). Almost a decade later, at the 10th International Conference on Bipolar Disorders (ICBD), presented in June 2013, Dr. Michael Bauer, M.D., Ph.D., president of International Group for the Study of Lithium Treated Patients (IGSLi), said very few people on long-term lithium develop Alzheimer’s disease (2). In spite of the time that has past, researchers do not understand lithium’s mechanism of action, or characteristics that would make it neuroprotective (see: “Is Lithium’s Effect on Brain Infection Electrical?).

**Parasitic Infections of the Brain Associated with Dementia**

In 2005, Drs. Osvaldo P. Almeida and Nicola T. Lautenschlager with the University of Western Australia’s School of Psychiatry and Clinical Neurosciences, reviewed the most frequent

**IGSLi’s Study on Lithium’s Neuroprotective Effect**

The IGSLi, founded in 1988 by Mogens Schou (Aarhus-Denmark), Bruno Müller-Oerlinghausen (Berlin-Germany), and Paul Grof (Ottawa-Canada), has selected Lithium’s Neuroprotective Effect as a long-term running project.
infectious causes of dementia that include Herpes virus, Toxoplasma gondii, Cryptococcus, Cytomegalovirus, syphilis, borrelia and cysticercosis (3). A review of the literature produced the following studies. Note: Toxocara has been added to this section containing dementia-causing pathogens:

**Category #1: Herpes Virus**

A virus is an infectious agent that replicates inside living cells of other organisms. Herpes viruses are a family of DNA viruses that cause disease in animals and humans. DNA viruses contain Deoxyribonucleic acid (DNA) and replicate using a DNA-dependent enzyme called polymerase. Eight herpesvirus types infect humans: herpes simplex viruses 1 and 2, varicella-zoster virus, EBV (Epstein-Barr virus), human cytomegalovirus, human herpesvirus 6, human herpesvirus 7, and Kaposi’s sarcoma-associated herpesvirus (4).

- **Linz, Germany (1995)**
  In 1995, C. Zachhuber led a team at the State Psychiatric Hospital Wagner-Jauregg in Linz, Germany in a study describing Alzheimer-type dementia in a 65 year-old female patient who was sero-positive for Herpes simplex virus. The patient died during the investigation and immuno-histochemical tests of brain tissue were positive for HSV type II. The authors concluded that if HSV encephalitis is suspected, an antiviral therapy must be administered immediately (5).

- **Manchester, UK (2011)**
  In 2011, Matthew A. Wozniak, a faculty member in the Life Sciences Department at the University of
Manchester, led a team of researchers in a study that determined antivirals reduce the formation of Alzheimer’s disease molecules (b-amyloid and phosphorylated tau) in cell cultures infected with Herpes Simplex Virus Type 1 (6).

**Category #2: Toxoplasma gondii**

Toxoplasma gondii is an intracellular (within a cell), obligate (reproduces inside a host cell), parasitic (living at the expense of a host) protozoan (single-celled eukaryote) that causes the disease toxoplasmosis.

- **Durango, Mexico (2006)**
  In 2006, Dr. Cosme Alvarado-Esquivel, faculty member at Juárez University in Durango, Mexico, led a study to determine the prevalence of T. gondii infection in a population of psychiatric patients in Durango City, Mexico. One hundred and thirty seven inpatients of a public psychiatric hospital and 180 controls were examined for the presence of IgG and IgM antibodies against T. gondii by enzyme-linked immunoassay. Researchers found a significantly higher prevalence of T. gondii in schizophrenic patients than the controls. Two of the patients in the study hospitalized for Alzheimer’s Disease were seropositive for T. gondii (7).

- **Afyonkarahisar, Turkey (2010)**
  In 2010, OY Kusbeci led a team of researchers at Afyon Kocatepe University in Afyonkarahisar, Turkey to investigate a possible association between toxoplasma infection and Alzheimer’s Disease (AD). Serum anti-Toxoplasma gondii IgG levels were examined in 34 patients with AD against
Association Between Infectious Diseases and Dementia

In their 2005 review of the most frequent infectious causes of dementia (3), Drs. Osvaldo P. Almeida and Nicola T. Lautenschlager explain that at the turn of the last century, infectious diseases represented an important cause of health morbidity and behavioral changes citing neurosyphilis as an example. They point out that with the advent of effective antibiotic treatment, the association between infectious diseases and dementia became increasingly less frequent. *This has led to the mistaken belief that Alzheimer’s and other dementias are incurable.* Dementias caused by pathogenic organisms are reversible with drug treatment.

*Case studies of infectious disease in patients with dementia emphasize the need to rule out all possible reversible causes.*

37 healthy individuals in a control group. The seropositivity rate for anti-T. gondii IgG antibodies among AD patients and control groups were 44.1% and 24.3%, respectively (8).

Category #3: Cryptococcus

Cryptococcus is a fungus that causes disease in humans as well as dogs, cats, cattle, sheep, goats, horses, wild animals, and birds. Soil, fowl manure, and pigeon droppings are sources of infection.

• **Springfield, Illinois (2004)**
  In 2004, Dr. Thomas A. Ala, M.D., a researcher at the Center for Alzheimer’s Disease and Related Disorders at Southern Illinois University (SIU) School of Medicine, led a team that evaluated a 70-year-old man with a three-year history of worsening dementia with a positive cryptococcal antigen test and a cerebral spinal fluid fungal culture that grew Cryptococcus neoformans. Note: C. neoformans and C.
gattii are cryptococcus species that cause Cryptococcosis, or cryptococcal disease that is a potentially fatal fungal disease. In humans, C. neoformans causes three types of infections:

- Wound or cutaneous cryptococcosis
- Pulmonary cryptococcosis
- Cryptococcal meningitis (CM).

The authors of the SIU study concluded:

1) CM should always be kept in the differential diagnosis of dementia
2) CM may be extremely insidious and difficult to diagnose
3) If one is to rule out unequivocally all possible reversible causes of dementia, one should perform a spinal tap (9).

• **Tampa, Florida (2009)**

In 2009, Dr. Mitchell Hoffman led a team of researchers at University of South Florida who identified cryptococcal meningitis in a sixty-two year-old male patient who had been diagnosed with Alzheimer’s disease three years before. After four months of treatment for meningitis, the patient made a complete neurological and cognitive recovery (10).
**Category #4: Cytomegalovirus**

Cytomegalovirus (CMV) is a member of the Herpes virus family described previously in this chapter.

- **Manchester, UK (2002)**
  In 2002, Woan Ru Lin, a researcher with the University of Manchester, led a team to search for herpes viruses in post mortem brain specimens from patients who had vascular dementia (VaD) using polymerase chain reaction technology. The researchers found a very high proportion of the VaD patients, 93%, harbored CMV DNA against controls (34%). They concluded that further studies are needed to determine whether or not the association of CMV with VaD is causal. (11)

- **Chicago, Illinois (2013)**
  In 2013, Dr. Nell S. Lurain, PhD, a researcher with Chicago’s Rush University Medical Center, led a team of researchers who searched for an association between cytomegalovirus (CMV) infection and clinical and pathological markers of Alzheimer using serum, cerebrospinal fluid (CSF), and cryopreserved lymphocytes from subjects in the Rush Alzheimer’s Disease Center Religious Orders Study. The authors found CMV antibody levels to be associated with neurofibrillary tangles (NFTs), or aggregates of hyper-phosphorylated tau protein that is considered to be a primary marker of Alzheimer’s Disease (12).
**Category #5: Treponema pallidum**

Treponema pallidum is a spirochete bacterium that causes diseases such as syphilis, bejel (nonvenereal syphilis), pinta (skin disease), and yaws (skin, bone and joint disease).

- **Toronto, Canada (2008)**
  
  In 2008, Dr. Michael Tso, M.D., led a team of researchers in a study that describes a 40 year-old Chinese man with neurosyphilis, a form of tertiary syphilis infection caused by the spirochete bacterium Treponema pallidum. The authors explain that the clinical course of syphilis can be divided into several distinct stages: primary, secondary, early latent, late latent and tertiary stages. If untreated in the latent phase, approximately 40% of patients develop tertiary syphilis. Manifestations of tertiary syphilis include cardiovascular syphilis, gummatous syphilis and neurosyphilis. Neurosyphilis includes cognitive and/or behavioral impairment as well as many other neurological and physical symptoms.

  Based on the investigations, the patient was diagnosed with neurosyphilis. Both Treponema Pallidum Agglutination Assay (TPPA) and Rapid Plasma Reagin (RPR) yielded positive serum results (RPR serum titre 1:64). A mini-mental status examination (MMSE) score and psychiatric symptoms were compatible with severe cognitive impairment and dementia. He was treated with Penicillin G 4 million units IV every 4 hours for 14 days, followed by Penicillin G procaine.
2.4 million units IM daily and probenecid 500 mg by mouth four times daily for 14 days. MMSE scores before and 8 weeks after treatment were 7/30 and 21/30 respectively. The patient recovered and was discharged after eight weeks (13).

**Ankara, Turkey (2011)**
In 2011, Dr. Süleyman Özselek, Assistant Director of the Department of Psychiatry at the Gu’lhane Military Medical Academy in Ankara, led a team of researchers in a study that describes a forty-five year old male patient with neurosyphilis. The study presents the authors’ search for of the patient’s dementia. Causes of primary dementia due to progressive degeneration of central nervous system were excluded due to development of the clinical picture in a relatively short time (1-2 years). The most effective treatment of neurosyphilis is high dose IV crystallized penicillin. Response to treatment should be monitored by cerebrospinal fluid (CSF) examination.

The authors explain that their case was consistent with parenchymatous neurosyphilis, a form of tertiary syphilis that develops 10 to 20 years after the primary infection. Parenchymatous neurosyphilist can mimic several neurological and psychiatric diseases. Neurological symptoms include tremor of lips, tongue, facial muscles and fingers, blunted affect and impairment of speech and writing. Unplanned and bizarre commitment of crime can be seen at the initial phase of the disease (14).

**Category #6: Borrelia**
Borrelia is a spirochete bacteria that causes borreliosis, a zoonotic (from animal to human, or from human to animal), vector-borne (a vector is an agent) disease transmitted primarily by ticks and lice.

**Lausanne, Switzerland (1994)**
In 1994, Dr. Judith Miklossy, a researcher with Lausanne’s University Institute of Pathology, wrote a chapter for a book titled *Alzheimer’s Disease: Therapeutic Strategies* (15)
questioning whether Alzheimer’s Disease is Spirochetosis. Judith presents Dr. Miguel Angel Pappolla M.D.,’s careful search for Borrelia burgdorferi in 18 Alzheimer’s Disease patients conducted in 1989 (16) and explains that although Pappolla et al., failed to support an association between Borrelia burgdorferi and AD, they did not rule out the possibility of another spirochete (16).

• **Lausanne, Switzerland (2004)**
In 2004, ten years after Dr. Judith Miklossy wrote her chapter titled “Alzheimer’s disease -- A spirochetosis?” she led a team at Lausanne’s University Institute of Pathology that used genetic and molecular analysis on Spirochetes of unidentified types and strains previously observed in the blood, CSF and brain of 14 AD patients and absent in 13 controls. In addition to positive phylogenetic identification of Borrelia burgdorferi, Borrelia antigens and genes were also co-localized with beta-amyloid deposits in the AD cases. The authors concluded that Borrelia burgdorferi may persist in the brain and be associated with amyloid plaques in AD (17).

**Category #7: Taenia**
Taenia is a tapeworm that infects livestock and humans. Tapeworms are responsible for human diseases called taeniasis and cysticercosis. Cysticercosis of the brain is called neurocysticercosis (NCC).

• **Mexico City, Mexico (2005)**
In 2005, Dr. Jesus Ramirez-Bermudez M.D., who recently spoke at Mexico’s 3rd International Symposium on Contro-
versies in Psychiatry, led a study at Mexico’s National Institute of Neurology and Neurosurgery that found dementia reversible in patients with neurocysticercosis, the scientific name for tape-worm infection of the brain. Ninety patients with untreated neurocysticercosis were given a cognitive assessment (Mini-mental State Examination, Neurobehavioral Cognitive Status Examination, and IQCODE) and were classified as having or not having dementia according to DSM-IV criteria.

Of the 90, 15.5% (fourteen) were classified as having dementia. All ninety patients were given albendazole and steroids for neurocysticercosis and remeasured for possible dementia six months later. After six months, 21.5% of the patients from the dementia group continued to have a full dementia disorder and 78.5% no longer fulfilled the DSM-IV criteria for dementia, although some of these patients still showed mild cognitive decline. The authors concluded that dementia occurs frequently in patients with untreated NCC, and it is reversible in most cases (18).

• **Ribeiro, Brazil (2012)**

In 2012, Dr. Corina Satler, faculty member and researcher at the University of Brasil in Ceilândia, led a team that published a case report about a 67-year-old woman with frontotemporal dementia (FTD) and a history of neurocysticercosis (NCC). The authors explain that frontotemporal dementia is the most common form of primary degenerative dementia after Alzheimer’s effecting people in middle age. This dementia occurs most commonly between the ages of 45 and 65 and is associated with atrophy and neuronal loss affecting the
temporal lobes of the brain. NCC can present a wide range of neuropsychiatric symptoms, that can be isolated (e.g. mental confusion, hallucinations, delirium, depressive of anxious symptoms) or constitute a well-characterized disorder (e.g. major depression, minor depression, intermittent depression, mania, panic disorder, general anxiety disorder, phobias, personality disorder and dementia. Additionally, patients with NCC often display cognitive impairment.

Mild to moderate cognitive dysfunction has been reported in up to 88% of NCC patients. The patient’s medical history revealed that in 1955, at the age of 11, she suffered from severe headaches, fainting and epilepsy and was diagnosed with NCC. According to her son, there are no records of treatment or drugs used to treat the infection. A CT scan showed more than 20 calcified lesions associated with NCC located bilaterally in the brain cortex and sub-cortical regions. In subsequent decades, she led a normal life. In 2004, at the age of 60, her son noticed significant changes in her behavior. In 2009, specialists at the Geriatric Medical Center at Brazil’s University Hospital diagnosed FTD and resolved the 65 year-old patient’s NCC. Although the patient no longer had NCC, she showed significant impairment in cognitive functioning and showed long response latency. Her son confirmed that her ability to use language had declined significantly (19).
• **Minas Gerais, Brazil (2012)**
  In 2012, Dr. C.L. Rosrigues, M.D. led a team of researchers in a cross-sectional study designed to evaluate cognitive decline in patients with the calcified form of C-NC, the largest subgroup of NC. Forty patients with C-NC were evaluated against 40 healthy controls. The authors concluded that independent of its phase, NC leads to a spectrum of cognitive abnormalities ranging from impairment in a single domain, to CIND, and occasionally, to dementia. These findings are more conspicuous during active vesicular phase and less prominent in calcified stages (20).

**Category #8: Toxocara**
Toxocara is a roundworm that infects dogs, cats and humans.

• **Tübingen, Germany (2002)**
  In 2005, Dr. Elke Richartz and Dr. Gerhard Buchkremer co-authored a report about a 65-year-old female patient showing cognitive deficits confirmed by psychometric tests had a positive antibody titre against Toxocara canis, a roundworm common in dogs. After treatment with Albendazole, the patient’s cognitive symptoms improved (21).

**Is Lithium’s Effect on Brain Infection Electrical?**
Professor Greg Tylka, a plant pathologist with Iowa State University may have inadvertently provided a clue concerning Lithium’s mechanism of action. Greg specializes in the management of soybean cyst nematode (SCN), a roundworm that is considered to be one of the most damaging plant parasites in the United States. In his *Soybean Cyst Nematode Field Guide* (22), Greg explains that nematodes like *alkaline soil*. Dr. George S. Roadcap, a hydrogeologist with Prairie Research Institute of the University
of Illinois at Urbana-Champaign has also found what he calls “diverse microbial communities” in extremely alkaline (pH > 12) groundwater (23).

The definition of alkaline is any substance having a base pH higher than 7. In solution, alkalinity is defined as a greater concentration of hydroxide ions (OH\(^{-}\)) than Hydrogen ions (H\(^{+}\)). Lithium, in the extreme upper left corner of the Periodic Table, is one of the most electropositive elements (24). If researchers have determined that large and small pathogens prefer alkalinity, is it possible that positively-charged Lithium ions have a neutralizing effect on pathogens that are electrically negative?

References


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