



Letter to the Editor

Kampō medicine and Muro disease (Amyotrophic Lateral Sclerosis and Parkinsonism-Dementia Complex): Postscript and Historical Footnote



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ABSTRACT

Western Pacific Amyotrophic Lateral Sclerosis and Parkinsonism-dementia Complex (ALS/PDC) is a disappearing neurodegenerative disease in three former high-incidence foci of the U.S. territory of Guam, Papua-Indonesia (New Guinea) and Kii Peninsula, Honshu Island, Japan (Muro disease). We report additional data that associate medicinal use of cycad seed to Muro disease in the southern Kozagawa focus of ALS/PDC. In the other two ALS/PDC-affected populations, cycad seed was used as a traditional topical medicine in New Guinea and Guam and, additionally, for food on Guam.

Dear Editor-in-Chief

We recently reported in these pages [1] the traditional practice of plant-based folk medicine (*Kampō*) in Mitogawa, a formerly isolated mountainous community with the highest historical incidence of amyotrophic lateral sclerosis (ALS) in the southern Kozagawa (Koza) focus of Muro disease in the Kii Peninsula of Honshu Island, Japan [2,3]. Mortality statistics for 1946-1965 revealed a rate of 14.3 per 1,000, which was 23.8 times higher than the average for Japan [3]. Kii ALS has been tentatively linked to oral use of neurotoxic cycad seed (*Cycas revoluta*) *sotetsu*, Japanese; *tie shu* or *su tie*, Chinese, meaning “iron tree”) in *Kampō* medicine [1]. As we previously reported, there is a seed-bearing cycad tree in the ALS epicenter of Mitogawa village (specifically, the Kosenji temple) [1], but we had no evidence for the historical medicinal use of *sotetsu* seed in this community. However, we have since learned from records of the late Marjorie Whiting [4], a nutritional scientist who resided in Mitogawa village for several months in the early 1960s (when the population was ~1300 persons), “that cycads were often grown as ornamentals” and “several [residents] described uses for cycads as medicine”; while “none of my informants had first-hand experience with medicinal use of the plant” [4]. Whiting’s notes record that a local public health nurse stated that “seed [was] used for the treatment of hemorrhoids”. In contrast to the use of cycad seed for food on Guam, in Mitogawa food use of “Cycad starch was never mentioned” during World II, when “Rice was rationed and various other starches as barley and sweet potatoes were substituted.” [4]. Whiting made these observations on behalf of the U.S. National Institute of Neurological Diseases and Blindness in dietary studies of people in the high-incidence ALS isolates in Guam (Marianas), Papua Indonesia (west New Guinea) and Japan’s Kii Peninsula, the location of Muro disease. Whiting’s observations strengthen the association between the traditional use of cycad seed as a folk medicine and the former very high incidence of ALS in Kozagawa.

The Japanese medical profession described ALS almost 150 years ago [5] but Muro disease (endemic ALS) is thought to have existed in the Koza region of the Kii peninsula for more than three centuries [6]. While description of the disease before the Meiji era (1868-1912) was

insufficient, a short description of a “mysterious paralysis in Koza of Kii Province” appears in the 17th century book titled *Honchō Koji In’nen Shū*, a collection of stories from the Tokugawa period [6,7]. In the Shōhō era (1644-48), the book states that “people who are ungrateful to their parents will not be allowed to walk on the road, and eventually suffer from being unable to move their legs.” [6]. Filial piety (*xiao*, Chinese; *kou*, Japanese) was a central Buddhist principle of Chinese Confucianism, and filial impiety was subject to harsh punishment in the Tang dynasty (618-907) [8], during which Confucian doctrine was brought to Japan and adopted as the official guiding philosophy of the Tokugawa (Edo) era (1603-1867). Under the Buddhist concept of Naraka, those who committed serious crimes, such as filial impiety, were sent to the Traditional Hell (*Diyu*, earth prison) of Chinese mythology, an underground maze with 18 levels and chambers of gruesome tortures conceived in the Tang Dynasty. Punishment for filial impiety was conducted in the Chamber of Iron Cycads (third layer, 鐵樹地獄), where guilty persons were hung on Iron trees (*Cycas* spp.) [9]. Whether fact, fantasy or fiction, the historical association between filial impiety, cycad exposure and paralysis is perhaps more than a remarkable coincidence given current understanding of the role of cycad genotoxins in the etiology of ALS [10].

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