

Letter to the Editor

Kampō medicine and Muro disease (Amyotrophic Lateral Sclerosis and Parkinsonism-Dementia Complex)



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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 Guam-USA, Papua-Indonesia and Kii Peninsula, Honshu Island, Japan. The latter includes two distinct ALS/PDC-affected regions (Hohara and Kozagawa), where the disorder is known as Muro disease. In Hohara, oral exposure to plant (cycad) neurotoxins used in traditional medical practice has been linked previously to Muro disease. We report new observations that link Kampō medicine to Muro disease in the southern Kozagawa focus. Oral exposure to cycad seed toxins is associated with all three foci of Western Pacific ALS/PDC.

Dear Editor-in-Chief

Muro disease is the local name given to the Amyotrophic Lateral Sclerosis and Parkinsonism-dementia Complex (ALS/PDC) that occurred formerly in high incidence in the northeastern Hohara and southern Kozagawa regions of the Kii Peninsula of Honshu Island, Japan [Fig. 1]. While Muro disease was observed to occur in families as well as sporadically, decades of research have failed to find a genetic etiology for Muro disease [1]. The decline in incidence and near disappearance of this neurodegenerative disorder has been attributed to changes in lifestyle, nutrition and oxidative stress [2], including cessation of ingestion of genotoxic chemicals in the seed of cycad plants (*Cycas* spp.) [3]. Cycad seed served as a traditional medicine not only in the Hohara region but also in the two other foci of Western Pacific ALS/PDC in Papua-Indonesia and Guam-USA [4], where food use of incompletely detoxified seed has been linked to ALS/PDC [5,6]. In the northeastern Kii focus of Muro disease, seed of *Cycas revoluta* Thunb. (*sotetsu*) was prescribed through the 1980s by *kitoshi* (shaman; “old-faith curer”) and dispensed by local pharmacies for treatment of various ailments, including diarrhea, dysmenorrhea, gonorrhoea, tuberculosis and neuralgia, in accord with published guidance [7]. Whether this traditional medical practice existed in the southern focus of Muro disease has been an open question.

We now report that plant-based folk medicine was also practiced in a centuries-old tradition of *furuisha* (“grand old doctor”) in Mitogawa, a mountainous community with the highest historical ALS incidence in the southern Kozagawa focus of Muro disease. In addition to the medicinal use of mountain herbs, *sotetsu* plants were present in Mitogawa, including a decades-old accessible female seed-bearing plant at the Shinto shrine at the center of the very high-risk ALS area of

Mitogawa village. Here, as in northeastern Kii, the former traditional healers followed Chinese-style Japanese folk medicine (*Kampō*) [7], which served these communities until the establishment of clinics practicing Western medicine. *Sotetsu* seed is no longer listed for use in *Kampō* or is found today in the Japanese Pharmacopoeia. Discontinuation of the medicinal use of *sotetsu* seed may have contributed to the disappearance of familial and sporadic Muro disease reported in a 1987–1991 survey of ALS among Kozagawa residents, emigrants and an immigrant [8]. This study showed that risk for ALS in later life could be acquired by childhood residency in Kozagawa through age 5 years, which is consistent with the early childhood treatment with a *sotetsu* tonic of a female resident in the Hohara focus of Muro disease who was diagnosed with ALS in her early twenties [3]. In this instance, her grandmother repeatedly administered to the young child a steep prepared from *sotetsu* seed (*su tie*, Mandarin, meaning ‘iron tree’) in the belief that the iron tree extract would strengthen her body and support her development. In sum, oral exposure to cycad toxins is a plausible etiology for ALS/PDC in Kii-Japan, as in Papua-Indonesia and Guam-USA.

Cycad seed contains a number of chemical substances with neurotoxic potential, including the principal toxin cycasin and beta-N-methylamino-L-alanine (L-BMAA). The concentration of cycasin in cycad flour was strongly associated with the incidence of ALS/PDC on Guam [6]. Cycasin is the glucoside of methylazoxymethanol (MAM), a potent DNA-damaging developmental neurotoxin. MAM is chemically related to hydrazines and nitrosamines that are found worldwide in products of natural and synthetic origin. The possible relevance of these MAM-related chemicals to the etiology of neurodegenerative disorders worldwide is discussed elsewhere [9].

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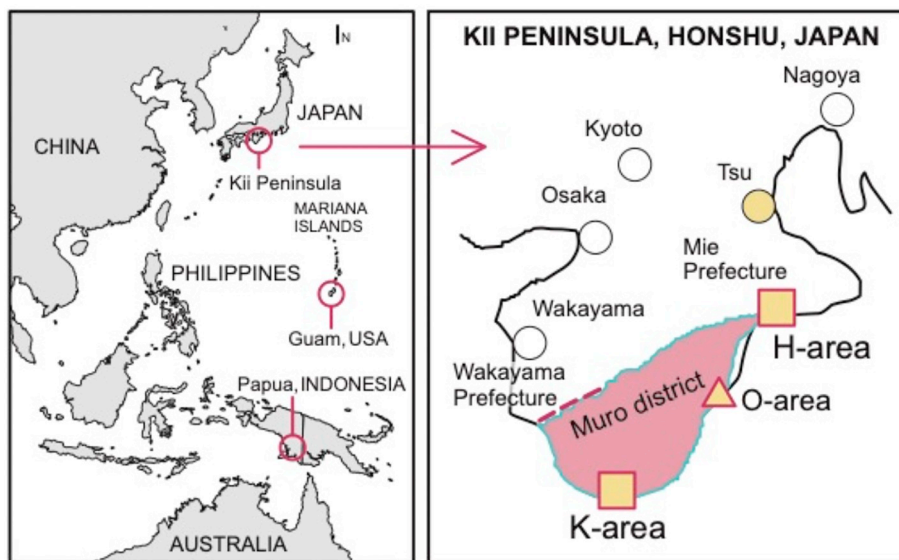


Fig. 1. Western Pacific ALS/PDC foci (left: red circles) and enlargement of the Kii Peninsula of Honshu Island, Japan (right). Muro District (colored area) includes the former high-incidence foci of ALS in the Hohara (H-area) of Mie Prefecture and the Kozagawa (K-area) of Wakayama Prefecture. A high prevalence of ALS (males > females) was first described in 1911 in Owase (O-area) and subsequently discovered in inland valleys of the H-area and in coastal and mountainous villages of the K-area. Five-year average incidence rates of Kii ALS per 100,000, age-adjusted to the Japanese population in 1985, were > 100 in 1950, < 40 in 1960 and < 20 in 2000 [1]. By 2009, the standardized incidence ratio (SIR) for ALS among males in Mie Prefecture (1.10; 95% CI = 0.69–1.67) matched the mean national SIR (1.08) covering 47 prefectures [10]. Between 1989 and 1993 in Kozagawa (K-area), the average annual incidence for males was 2.23/100,000, with the highest incidence rate of 9.3/100,000 in a single then-isolated mountainous village of Mitogawa [8]. Modified from [1]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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