

Reply to: Questioning the cycad theory of Kii ALS–PDC causation



We read with great interest the Correspondence to our recent Review (Menšíková, K. et al. Endemic parkinsonism: clusters, biology and clinical features. *Nat. Rev. Neurol.* **19**, 599–616 (2023)¹) by Kokubo and colleagues (Kokubo, Y., Morimoto, S. & Yoshida, M. Questioning the cycad theory of Kii ALS–PDC causation. *Nat. Rev. Neurol.* <https://doi.org/10.1038/s41582-024-00936-0> (2024)²). We are aware that Kokubo – together with the late S. Kuzuhara – systematically studied amyotrophic lateral sclerosis–parkinsonism–dementia complex (ALS–PDC) on the Kii Peninsula for more than 30 years. They authored and co-authored numerous papers about this endemic disease, some of them with one of us (R.S.). We therefore considered the comments raised by Kokubo et al. carefully, and here we respond to the questions that they have raised.

Kokubo et al. state that the use of cycad seed in herbal and folk medicine, and as a tonic in children, is very rare. However, in the north-eastern Kii (Hohara) focus of ALS–PDC, the seed of *Cycas revoluta* was prescribed throughout the 1980s by *kitoshi* (folk medicine practitioners) and dispensed by local pharmacies for the oral treatment of various ailments, including diarrhoea, dysmenorrhoea, gonorrhoea, tuberculosis and neuralgia, in accordance with published guidance³. In 1986, one of us (P.S.) personally met with a *kitoshi* in Owase, Mie prefecture, who prescribed cycad seed (*sotetsu*) for a fictional gastrointestinal problem; a local pharmacy that dispensed *sotetsu* seed for medicinal purposes is depicted in the BBC video *The Poison That Waits*. Importantly, older patients with ALS–PDC might not remember using this medicine or being dosed with *sotetsu* tonic during infancy, another local practice that is documented in the BBC video.

O. Hatashin – the nephew of S. Yokoi – authored a book on the life of his uncle during his hiding on Guam⁴, and he recorded that Yokoi developed an effective method to remove most or all of the poison from cycad seed. On his return to Japan in 1972, Yokoi was examined by a neurologist who noted some muscle wasting in his palms and neurogenic

patterns on electromyographic examination of his leg muscles. Unfortunately, Yokoi's spinal cord was not examined at autopsy⁵.

Kokubo et al. are correct in their assertion that ALS–PDC does not occur on the Japanese island of Amami Oshima. However, in the Ryukyu Islands, cycad seed and sago are subjected to prolonged fermentation and repeated washing, which – unlike the preparation method used on Guam by families affected by ALS–PDC – detoxifies the plant material⁶.

The proposed cycad toxin-related origin of the retinal and cerebellar pathology reported in individuals with ALS–PDC from Kii (Japan) or Guam has been described in detail by Spencer⁷. Methylazoxymethanol (the aglycone of cycasin) is a neurodevelopmental genotoxin that forms persistent neuronal DNA adducts in mouse brains and is associated with human neurodegenerative disease⁸, but, to our knowledge, these adducts have not been looked for in the brains of patients with ALS–PDC.

We would like to reiterate our conclusion that the pathogenesis of Kii ALS–PDC remains to be determined and could involve multiple factors. We feel that we did not question the conviction of S. Kuzuhara and his team, but presented data that support the cycad theory – one that is consistent with the probable aetiology of ALS–PDC on Guam.

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Competing interests

The authors declare no competing interests.

Related links

The Poison that Waits: <https://vimeo.com/1621281>