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Questioning the cycad theory of Kii ALS–PDC causation

In a recent Review by Menšíková and colleagues (Menšíková, K. et al. Endemic parkinsonism: clusters, biology and clinical features. *Nat. Rev. Neurol.* **19**, 599–616 (2023)[1]), we have identified several statements in relation to the Kii amyotrophic lateral sclerosis–parkinsonism–dementia complex (ALS–PDC) that conflict with our own observations.

There are several misconceptions and errors that should not be overlooked regarding epidemiology, clinical features, neuropathology and genetics, especially in the section on causative factors, in which the authors assert that extracts from highly toxic cycad seeds were used in traditional medicine to treat diseases such as diarrhoea, dysmenorrhoea, gonorrhoea and haemorrhoids and were given to children in the belief that they would strengthen their bodies and support their development. However, Y.K. has worked directly with many patients with ALS–PDC and their families on the Kii Peninsula for over 30 years and also resided in a multi-occurrence area for 3 years, and he has noted that no residents in areas of high ALS–PDC occurrence eat or drink cycad. The use of cycad in herbal and folk medicine is very rare and seems to be unrelated to the development of ALS–PDC. Furthermore, it is uncommon to use cycad as a tonic in children.

Additional findings cast doubt on the proposed link between cycad ingestion and ALS–PDC. First, S. Yokoi was a Japanese soldier who survived for 28 years in the jungles of Guam and developed symptoms of parkinsonism in his later years. He was suspected to have PDC because he had a regular cycad diet, although pathology showed Parkinson disease rather than PDC[2]. Second, the Amami Okinawa region of Japan is a group of islands located between Kyushu and Taiwan, approximately 1,000 km from the Kii Peninsula. Cycad was historically used as a food in this region and is still used in porridge, miso and other dishes[3,4]. However, there is no evidence of a high ALS frequency in these areas and no reports of ALS–PDC with tau pathology. Last, we previously analysed β-*N*-methylamino-L-alanine (produced by cyanobacteria, one of the neurotoxins associated with cycads) in the brains of patients with Kii ALS–PDC, using mass spectrometry, but found no evidence of expression[5].

The Menšíková et al. Review[1] provided some circumstantial evidence that links cycads to ALS–PDC; for example, the cerebellar and retinal dysplasia associated with the condition was reproduced in newborn rodents exposed in utero to the cycad toxins cycasin and methylazoxymethanol[6]. However, we are unaware of any direct evidence, such as detection of methylazoxymethanol in the brains of patients, that cycad is responsiblefor ALS–PDC.

In summary, Y.K. has found no evidence of a causative role for cycad in Kii ALS–PDC, and the cycad theory has no meaning to local residents. On the basis of our findings, we therefore conclude that cycad is not the cause of Kii ALS–PDC. Additional correspondence regarding epidemiology, clinical features, neuropathology and genetics has been provided directly to the corresponding author of Menšíková et al.'s Review.

There is a reply to this letter by Menšíková, K. et al. *Nat. Rev. Neurol.* https://doi.org/10.1038/s41582-024-00938-y (2024)

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Competing interests

The authors declare no competing interests.