

WESTERN PACIFIC ALS-PARKINSONISM-DEMENTIA COMPLEX: GENETIC OR TOXIC ETIOLOGY? DISCUSSING A GENETIC ETIOLOGY

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Synopsis: (slide 1) The ALS/Parkinsonism-dementia complex (ALS/PDC) is a long latency polyproteinopathy of three Western Pacific isolates, and its diverse immunopathology is expressed as classical ALS, atypical parkinsonism and Alzheimer type dementia. On Guam during the past 40 years, its incidence has declined, its age at onset has increased, and its predominant phenotype has altered from ALS to dementia. Identifying its cause will advance understanding and the management of neurodegeneration.

History

(slide 2) ALS/PDC began before industrialization and modern times and was described in the Ki peninsula of Japan in the sixteenth century and recorded in Spanish death certificates of Guam in the early 1800s. But it was not until after World War II that ALS was identified to be common in young Chamorros of Guam and a second syndrome of atypical parkinsonism, like postencephalitic parkinsonism, and dementia was identified in other members of their families.

(slide 3) With this awareness, Japanese neurologists recognized the same illness in the families of mountain villages in the Kii peninsula, and Gajdusek identified it in the villages and families of primitive headhunting tribe people living on mud flats of the coastal plain in West New Guinea (WNG). The ethnicities, geography, cultures and geochemistry were quite different in each locale, and there was no obvious risk factor to account for the same disease in these small and widely separated Pacific isolates.

(slide 4) On Guam ALS/PDC has a wide range in age at onset from 15 to 94 years and in affected families, the onset of ALS is younger than atypical parkinsonism with dementia (PDC), and dementia without parkinsonism does not begin until late life. The disease is usually fatal in 3 to 5 years but survival varies and may be only 6 months or more than 30 years.

(slide 5) There are no distinctive pathological features that distinguish between phenotypes, and all patients have an identical immunopathology with accumulations of 3R and 4R tau, beta amyloid, alpha synuclein, ubiquitin and TDP-43, as occur in atypical parkinsonism, Alzheimer's disease and ALS elsewhere. Study of asymptomatic Guamanians with latent disease has shown its pathology slowly spreads throughout the brain, and steadily increases in intensity to become widespread and severe by late life.

Familial clustering of ALS/PDC; Genetic or environmental?

(slide 6) Because ALS/PDC has occurred in successive generations in all three Pacific locales, the disease was initially thought to be genetic. But subsequent studies on Guam and in Japan challenge that hypothesis and none support it.

- 1) Pedigrees of affected families are unlike those of Mendelian inheritance,
- 2) Only residents of the three Pacific locales are affected by the disease which does not affect those of the same ethnicity living in other places
- 3) Migrants of other ethnicity taking up residence on Guam have developed ALS and PDC and American soldiers serving on Guam in 1944 and 1945 for only 1 to 2 months have developed ALS 40 years later while living in New York city.
- 4) During the past 60 years on Guam the incidence of the disease has steadily declined, its age in onset has increased and the disease is about to end, as it has in West New Guinea and maybe in Japan.
- 5) Genome studies of Guamanian and Japanese families are unsuccessful in identifying significant gene abnormalities, except for a large genotyping of single nucleotide polymorphisms (SNPs) on Guam by Schellenberg in 2009. He and his colleagues conclude that changes in the tau region contribute only a small risk of ALS/PDC and are not likely to cause it.

Although I was asked to advocate for the genetic hypothesis of ALS/PDC, there is presently nothing that favors it, and I believe its etiology is primarily environmental and relates to a hazard of the place one lives and one's family.

Studies in Umatac

(slide 7) Umatac is the smallest of Guam's 15 villages with a population of 1,000 in 5 families. The Chamorro civilization began here in southern Guam 4000 years ago and it was discovered by Magellan who landed there in 1521. It is the epicenter of ALS/PDC which Chamorros call *lytico-bodig* and reliable folktale accounts indicate paralysis (ALS) began in one of its 5 families (the Q family) in the early 1800s. Of more than 1000 cases of ALS/PDC identified on Guam by National Institutes of Health (NIH) scientists since 1940, 18 % are from this village. The disease began to alter in those born in 1920 and steadily declined by birth year until 1946 when the last case of PDC began. Although many adults of all the Umatac families suffered ALS, PDC or dementia before World War II, none of their children born after 1940 have developed it, though they are now at the same age risk as their parents.

Because the cause of ALS/PDC must have been most prominent in the 3 valleys and 6 square miles of the Umatac district, many studies to identify its cause have been conducted there.

(Video with Oliver Sacks in Umatac)

(slide 8) In the early 1980s with aluminum specialist Crapper McLachlan of Toronto, we tested the minerals and metals of soils and waters in Umatac and other parts of Guam. We found them to be normal and not different from

other tropical islands including Jamaica and Palau. Our findings, confirmed by others did not confirm Gajdusek's hypothesis for a geochemical cause of ALS/PDC.

The role of cycad seed toxins in the etiology of ALS/PDC has been controversial since they were first suggested as important by Kurland, Whiting and Fosberg in the 1950s.

(slide 9) After 1986, with Drs. Spencer and Duncan we studied the role of cycad-derived BMAA in Chamorro foods and were disappointed when its values in cycad products were low and it seemed unlikely to be the agent causing ALS/PDC.

(slide 10) In 2002, with Drs. Cox, Sacks and McGeer we investigated the role of BMAA in flying foxes that had fed on cycad seeds and were eaten by Chamorros. McGeer showed BMAA was a weak toxin and others were unable to confirm BMAA in brain tissues, as Cox claimed to be present. These facts lead us to doubt that hypothesis.

We have read Dr. Spencer and Kisby's recent paper indicating that cycasin, another cycad toxin can be genotoxic and cause ALS/PDC. I am interested to hear him speak of it this afternoon.

(slide 11) During the 1990s medical anthropologist Keck interviewed residents of Umatac and the adjacent village of Merizo to detect differences in individual and family life styles, food preferences and habits that could account for extreme differences in the prevalence of ALS and PDC between them. She reported that her "anthropological analysis of changes in Chamorro history, culture and environment do not show differences between the two adjacent villages of Umatac and Merizo."

(slide 12) Despite all these many negative investigations, there remains a clue that may explain the etiology of ALS/PDC.

It is a linear retinopathy with the appearance of a worm migration in the retinal pigment epithelium at the back of the eye. We refer to it as linear retinal pigment epitheliopathy (LRPE) and it is symptomatic, bilateral in 40% and likely to be blood borne. Once established, its meandering tracks do not alter or progress. LRPE is present in one half of patients with ALS/PDC and predicts the neurological disease may occur in those who are asymptomatic when it is recognized by indirect ophthalmoscopy. It is present also in ALS/PDC patients of the Kii peninsula but is not identified by ophthalmologists, parasitologists or veterinarians in any other part of the world. We regard it as a marker of the etiological event of ALS/PDC, a hypothesis that seems as unlikely as cycad seeds and flying foxes.

Conclusion

(slide 13) I feel it is important that we continue all efforts to crack this mystery and discover the cause of ALS/PDC which neuropathologist Harry Zimmerman first recognized in 1946 and referred to as an "obscure malady". And I am optimistic that clarifying its cause will provide understanding of pathogenesis, and can help to end neurodegenerative diseases of the world, as has happened on Guam and in New Guinea.

I congratulate Professor Spencer and Glen Kisby's new hypothesis of genotoxicity which continues that effort.

References

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