frontiers in Psychiatry

GENERAL COMMENTARY
published: 06 August 2021
doi: 10.3389/fpsyt.2021.653624

Commentary on Singh et al. (2020) Postzygotic Somatic Mutations in the Human Brain Expand the Threshold-Liability Model of Schizophrenia

Peter S. Spencer[1]* *and Glen E. Kisby*[2]

[1] *Department of Neurology, School of Medicine, and Oregon Institute of Occupational Health Sciences, Oregon Health & Science University, Portland, OR, United States,* [2] *Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific Northwest, Western University of Health Sciences, Lebanon, OR, United States*

Keywords: schizophrenia, amyotrophic lateral sclerosis, environmental somatic mutagen, brain DNA damage, methylazoxymethanol

A Commentary on

Postzygotic Somatic Mutations in the Human Brain Expand the Threshold-Liability Model of Schizophrenia
by Singh, S. M., Castellani, C. A., and Hill, K. A. (2020). Front. Psychiatry 11:587162. doi: 10.3389/fpsyt.2020.587162

OPEN ACCESS

Edited by:
Patrick E. Williams, University of Kansas, United States

Reviewed by:
Jurjen Luykx, University Medical Center Utrecht, Netherlands

***Correspondence:**
Peter S. Spencer
spencer@ohsu.edu

Specialty section:
This article was submitted to Behavioral and Psychiatric Genetics, a section of the journal Frontiers in Psychiatry

Received: *14 January 2021*
Accepted: *14 July 2021*
Published: *06 August 2021*

Citation:
Spencer PS and Kisby GE (2021) Commentary on Singh et al. (2020) Postzygotic Somatic Mutations in the Human Brain Expand the Threshold-Liability Model of Schizophrenia. Front. Psychiatry 12:653624. doi: 10.3389/fpsyt.2021.653624

INTRODUCTION

Singh and colleagues note that the mammalian brain has a high degree of mosaicism likely caused by postzygotic genetic and epigenetic alterations that may contribute to most multifactorial and complex neurological disorders, for which the authors use schizophrenia to exemplify. They suggest that schizophrenia arises from a sufficient level of inherited, or inherited plus acquired, brain somatic mutations and/or epimutations, a model with particular relevance they suggest to disorders with neurodegeneration and neurodevelopmental manifestation. We wish to extend this model by noting that acquired somatic mutations/epimutations *in the absence of any inherited predisposition* may be sufficient to trigger a neurodegenerative disorder with neurodevelopmental manifestations and links to schizophrenia. Additionally, in accord with the authors' analysis, we note the importance of environmental mutagens as potential triggers of somatic mutation/epimutations that result not only in cancer but also neurodegenerative disease.

MOTOR SYSTEM DEGENERATION

The neurodegenerative disease of interest here is the Western Pacific Amyotrophic Lateral Sclerosis and Parkinsonism-Dementia Complex (ALS/PDC), which is known principally in residents of and migrants to and from the former disease hot spots of Guam Island (among Chamorros) and Kii Peninsula, Honshu Island (among Japanese) (1). Once thought to have a genetic origin, later a changing environmental component that explained its decline, and subsequently, with the absence of a characteristic genotype and disappearance of the disease on Guam, considered to have a prominent if not exclusive exogenous etiology. Evidence points to the traditional use of cycad seed for food and/or medicine, practices that disappeared in concert with post-WW II modernization.

On Guam, cycad seed, and the food derived therefrom, contain methylazoxymethanol (MAM) β-D-glucoside (cycasin) and β-*N*-methylamino-L-alanine (L-BMAA), an uncommon amino acid (2). These substances are both metabolized to the mutagen formaldehyde (1), which from endogenous sources and/or from exogenous exposure is linked to both brain cancer and sporadic ALS (3). Accordingly, MAM, the active form of the major cycad toxin, is a genotoxic agent with both carcinogenic and neurotoxic properties (1). There is a strongly significant correlation between the concentration of cycasin (but not L-BMAA) in cycad flour prepared Chamorro-style and the incidence of ALS and P-D among males and females on Guam (4). Additionally, MAM disrupts retinal and cerebellar development, which respectively anticipate and attend the adult onset of ALS/PDC (5). Most significantly, for present purposes, MAM is widely used experimentally to produce a rodent model of schizophrenia. In female rats, the administration of MAM on gestational day 17 disrupts brain development leading to histological, neurophysiological and behavioral deficits analogous to those of schizophrenia (6, 7). How closely the rodent MAM model reproduces the neuropathological and behavioral features of schizophrenia is unknown.

SCHIZOPHRENIA AND ALS

While rare cases have linked schizophrenia and Western Pacific ALS/PDC (8, 9), there is growing clinical, epidemiological and biological evidence of an association between ALS and psychotic illness (10), particularly schizophrenia (11). Westphal (12) observed that the paranoid and manic-depressive states of schizophrenia were associated with ALS but considered the neuropsychological and motor system disorders to be unrelated. Wechsler and Davison (13) reported that mental symptoms were due to cortical degenerative changes associated with ALS. Turner and colleagues (14) found that schizophrenia may represent a risk factor for ALS (OR 5.0). Howland (15) noted several cases in which schizophrenia occurred in ALS patients. Register-based nationwide studies show a higher occurrence of schizophrenia up to 1–5 years before and 2–5 years after ALS diagnosis (16). The coexistence of ALS and schizophrenia has been interpreted as indicative of a shared polygenic basis (11), and GWAS studies support a genetic correlation between the two conditions (11, 17). Neuropsychiatric symptoms other than schizophrenia, including obsessive-compulsive disorder, autism, and alcoholism, occur more frequently in first- or second-degree relatives of ALS patients with and without *C9orf72* expanded repeats (18, 19). Disturbances in motor neuron function have been demonstrated in schizophrenia (20–22).

MOLECULAR MECHANISMS

We have discussed elsewhere evidence that MAM experimentally induces early epigenetic changes that coincide with DNA damage and cell-cycle reactivation, evidence for which is seen in the ALS/PDC brain (23–25). MAM disrupts the cell cycle presumably by inducing DNA damage *via* methylation of guanine (i.e., *N*7 methyl and/or O^6-methyl adducts) that inhibits DNA replication during S phase (26) and disrupts neuroepithelial cells undergoing their final mitosis (27). Some of the early changes induced by MAM in somatic cells include nucleoprotein structural alterations, mitotic abnormalities, and induction of polyploidy (28) as well as retinoblastoma (Rb) gene mutations, which lead to the development of intraocular neoplasms (29, 30). Expression of the retinoblastoma gene is also altered in the prefrontal cortex of rats treated developmentally with MAM (31) and in human neuroprogenitor cells (hNPCs) 24 h after acute treatment with the genotoxin (32). L-BMAA also induces cell-cycle dysregulation in embryonic rat striatal neurons (1, 33).

DISCUSSION

Whether MAM-induced DNA damage and/or epigenetic changes are the initial event(s) that trigger the cell-cycle changes is presently unknown, but it is clear that this genotoxin induces somatic cell changes that are linked with both experimental schizophrenia and neurodegeneration in the form of Western Pacific ALS/PDC. Given the absence of any known genetic susceptibility factor for this prototypical neurodegenerative disease—one that often has subclinical evidence of developmental cerebellar and retinal dysplasia (5)—it is reasonable to propose that exposure to an environmental mutagen/epimutagen alone (notably MAM) is sufficient to trigger the disorders. Given this conclusion, we extend the model proposed by Singh and colleagues to include *environmentally acquired* somatic mutations/epimutations as sufficient to trigger a neurodegenerative disorder with neurodevelopmental manifestations and links to schizophrenia. The corollary emphasizes the need to search for early-life exposure to environmental mutagens/epimutagens in related spontaneous neurodegenerative disorders, including ALS, atypical Parkinson syndromes such as Progressive Supranuclear Palsy, and Alzheimer disease (34).

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

Research was supported in part by NIH-NIEHS grant U19ES011384 (PS and GK) and NIH 1R01ES026225 (GK). Stem cell research was supported by Illumina and Western University of Health Sciences (GK).

REFERENCES

1. Spencer PS, Palmer VS, Kisby GE. Western Pacific ALS-PDC: evidence implicating cycad genotoxins. *J Neurol Sci.* (2020) 419:117185. doi: 10.1016/j.jns.2020.117185
2. Kisby GE, Ellison M, Spencer PS. Content of the neurotoxins cycasin (methylazoxymethanol β-D-glucoside) and BMAA (β-*N*-methylamino-L-alanine) in cycad flour prepared by Guam Chamorros. *Neurology*. (1992) 42:1336–40. doi: 10.1212/WNL.42.7.1336
3. Rana I, Rieswijk L, Steinmaus C, Zhang L. Formaldehyde and brain disorders: a meta-analysis and bioinformatics approach. *Neurotox Res.* (2021) 20:320. doi: 10.1007/s12640-020-00320-y
4. Román GC. Neuroepidemiology of amyotrophic lateral sclerosis: clues to aetiology and pathogenesis. *J Neurol Neurosurg Psychiatry.* (1996) 61:131–7. doi: 10.1136/jnnp.61.2.131
5. Spencer PS. Etiology of retinal and cerebellar pathology in Western Pacific Amyotrophic Lateral Sclerosis and Parkinsonism-Dementia Complex. *Eye Brain.* (2020) 12:97–104. doi: 10.2147/EB.S260823
6. Lodge DJ, Grace AA. Gestational methylazoxymethanol acetate administration: a developmental disruption model of schizophrenia. *Behav Brain Res.* (2009) 204:306–12. doi: 10.1016/j.bbr.2009.01.031
7. Jones CA, Watson DJ, Fone KC. Animal models of schizophrenia. *Br J Pharmacol.* (2011) 164:1162–94. doi: 10.1111/j.1476-5381.2011.01386.x
8. Yase Y, Matsumoto M, Azuma K, Nakai Y, Shiraki H. Amyotrophic lateral sclerosis: association with schizophrenic symptoms and showing Alzheimer's tangles. *Arch Neurol.* (1972) 27:118–28. doi: 10.1001/archneur.1972.00490140022005
9. Shindo A, Ueda Y, Kuzuhara S, Kokubo Y. Neuropsychological study of amyotrophic lateral sclerosis and parkinsonism-dementia complex in Kii peninsula, Japan. *BMC Neurol.* (2014) 14:151. doi: 10.1186/1471-2377-14-151
10. Zucchi E, Ticozzi N, Mandrioli J. Psychiatric symptoms in Amyotrophic Lateral Sclerosis: beyond a motor neuron disorder. *Front Neurosci.* (2019) 13:175. doi: 10.3389/fnins.2019.00175
11. McLaughlin R, Schijven D, van Rheenen W, van Eijk KR, O'Brien M, Kahn RS, et al. Project MiniE GWAS Consortium, Schizophrenia Working Group of the Psychiatric Genomics Consortium Genetic correlation between amyotrophic lateral sclerosis and schizophrenia. *Nat Commun.* (2017) 8:14774. doi: 10.1038/ncomms14774
12. Westphal A. Schizophrene Krankheitsprozesse nnd amyotrophische Lateralsklerose. *Arch fiir Psychlat.* (1925) 74:810. doi: 10.1007/BF01814189
13. Wechsler IS, Davison C. Amyotrophic lateral sclerosis with mental symptoms. A clinicpathologic study. *Arch Neurol Psychiatr.* (1932) 27:859–80. doi: 10.1001/archneurpsyc.1932.02230160100010
14. Turner MR, Goldacre R, Talbot K, Goldacre MJ. Psychiatric disorders prior to amyotrophic lateral sclerosis. *Ann Neurol.* (2016) 80:935–8. doi: 10.1002/ana.24801
15. Howland RH. Schizophrenia and amyotrophic lateral sclerosis. *Comp Psychiatry.* (1990) 31:327–36. doi: 10.1016/0010-440X(90)90039-U
16. Longinetti E, Mariosa D, Larsson H, Ye W, Ingre C, Almqvist C, et al. Neurodegenerative and psychiatric diseases among families with amyotrophic lateral sclerosis. *Neurology.* (2017) 89:578–85. doi: 10.1212/WNL.0000000000004179
17. Restuadi R, Garton FC, Benyamin B, Lin T, Williams KL, Vinkhuyzen A, et al. Polygenic risk score analysis for amyotrophic lateral sclerosis leveraging cognitive performance, educational attainment and schizophrenia. *Eur J Hum Genet.* (2021) 21:885. doi: 10.1038/s41431-021-00885-y
18. Byrne S, Heverin M, Elamin M, Bede P, Lynch C, Kenna K, et al. Aggregation of neurologic and neuropsychiatric disease in amyotrophic lateral sclerosis kindreds: a population-based case-control cohort study of familial and sporadic amyotrophic lateral sclerosis. *Ann Neurol.* (2013) 74:699–708. doi: 10.1002/ana.23969
19. O'Brien M, Burke T, Heverin M, Vajda A, McLaughlin R, Gibbons J, et al. Clustering of neuropsychiatric disease in first-degree and second-degree relatives of patients with amyotrophic lateral sclerosis. *JAMA Neurol.* (2017) 74:1425–30. doi: 10.1001/jamaneurol.2017.2699
20. Crayton JW, Meltzer HY, Goode DJ. Motoneuron excitability in psychiatric patients. *Biol Psychiatry.* (1977) 12:545–61.
21. Crayton JW, Meltzer HY. Degeneration and regeneration of motor neurons in psychotic patients. *Biol Psychiatry.* (1979) 14:803–19.
22. Goode DJ, Manning AA. Specific imbalance of right and left sided motor neuron excitability in schizophrenia. *J Neuro Neurosurg Psychiatry.* (1988) 51:626–9. doi: 10.1136/jnnp.51.5.626
23. Wang W, Bu B, Xie M, Zhang M, Yu Z, Tao D, Neural cell cycle dysregulation and central nervous system diseases. *Prog Neurobiol.* (2009) 89:1–17. doi: 10.1016/j.pneurobio.2009.01.007
24. Stone JG, Siedlak SL, Tabaton M, Hirano A, Castellani RJ, Santocanale C, et al. The cell cycle regulator phosphorylated retinoblastoma protein is associated with tau pathology in several tauopathies. *J Neuropathol Exp Neurol.* (2011) 70:578–87. doi: 10.1097/NEN.0b013e3182204414
25. Husseman JW, Nochlin D, Vincent I. Mitotic activation: a convergent mechanism for a cohort of neurodegenerative diseases. *Neurobiol Aging.* (2000) 21:815–28. doi: 10.1016/S0197-4580(00)00221-9
26. Matsumoto H, Spatz M, Laqueur GL. Quantitative changes with age in the DNA content of methylazoxymethanol-induced microencephalic rat brain. *J Neurochem.* (1972) 19:297–306. doi: 10.1111/j.1471-4159.1972.tb01339.x
27. Cattaneo E, Reinach B, Caputi A, Cattabeni F, Di Luca M. Selective *in vitro* blockade of neuroepithelial cells proliferation by methylazoxymethanol, a molecule capable of inducing long lasting functional impairments. *J Neurosci Res.* (1995) 41:640–7. doi: 10.1002/jnr.490410510
28. Zedeck MS, Sternberg SS, Yataganas X, McGowan J. Early changes induced in rat liver by methylazoxymethanol acetate: mitotic abnormalities and polyploidy. *J Natl Cancer Inst.* (1974) 53:719–24. doi: 10.1093/jnci/53.3.719
29. Hawkins WE, Fournie JW, Overstreet RM, Walker WW. Intraocular neoplasms induced by methylazoxymethanol acetate in Japanese medaka (*Oryzias latipes*). *Natl Cancer Inst.* (1986) 76:453–65.
30. Rotchell JM, Blair JB, Shim JK, Hawkins WE, Ostrander GK. Cloning of the Retinoblastoma cDNA from the Japanese medaka (*Oryzias latipes*) and preliminary evidence of mutational alterations in chemically-induced retinoblastomas. *Gene.* (2001) 263:231–7. doi: 10.1016/S0378-1119(00)00566-7
31. Merker R, Kisby GE, Moore H. Abnormal neonatal and adult gene expression patterns in the hippocampus and prefrontal cortex of offspring of rat dams exposed to methylazoxymethanol acetate at embryonic day 17. *Soc. Neurosci*. (2009).
32. Kisby GE, Chlebowski AC, Grygoryev D, Carbone L, Davis B, Nevonen KA, et al. The neurodevelopmental toxin methylazoxymethanol (MAM) induces DNA methylation changes in differentiated human iPSC-derived neuroprogenitor cells (hNPCs). *Soc Neurosci*. (2018) 196:03/A3.
33. Pierozan P, Karlsson O. Mitotically heritable effects of BMAA on striatal neural stem cell proliferation and differentiation. *Cell Death Dis.* (2019) 10:478. doi: 10.1038/s41419-019-1710-2
34. Spencer PS. Hypothesis: etiologic and molecular mechanistic leads for sporadic neurodegenerative diseases based on experience with Western Pacific ALS/PDC. *Front Neurol.* (2019) 10:754. doi: 10.3389/fneur.2019.00754

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.