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Malnutrition and childhood epilepsy in developing countries

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A high prevalence of epilepsy in children is frequently found in developing countries. Though high rates of acquired brain injury may contribute, the possibility that malnutrition may lower seizure threshold has rarely been examined. This review suggests potential biochemical mechanisms that could adversely affect seizure threshold, particularly the effect of malnutrition on inhibitory neurotransmitters and electrolytes. Supporting evidence from animal research and epidemiological findings in children are discussed.

Key words: malnutrition; epilepsy; children; developing country.

INTRODUCTION

Many epidemiological studies of childhood epilepsy from developing countries have shown high prevalence rates[1], sometimes as high as four times those in the West[2]. Though the disparity in findings may be due to differences in case definition and ascertainment, studies that used the same method at several sites have found marked differences in prevalence. Rwiza *et al.*, in Tanzania[3] found prevalence rates varying from 5.1 to 37.1 per 1000 between villages and Durkin[4] found prevalence rates ranging from 5.8 per 1000 in Jamaica to 15.5 per 1000 in Pakistan, using an identical methodology on both sites. This suggests real geographical differences in prevalence within and between countries.

Though few studies from developing countries have examined aetiological factors for childhood epilepsy there is evidence of profound differences from Western populations. Case series from Tanzania[5] and Pakistan[6] emphasized the importance of CNS infection and perinatal complications. Some studies have demonstrated the importance of specifically tropical infections such as malaria[7] and arthropod-bourne encephalitis[8], others emphasize high rates of infections also found in the West such as bacterial meningitis[9], while others[10,11] draw attention to epilepsy-causing parasites such as neurocysticercosis which, though not specifically tropical, are diseases of poverty.

Studies that include adults also implicate head injury[12], but the spectrum of aetiology changes with age and findings in adults are of limited relevance to children. No cause can be identified for epilepsy in 60–90% of cases[13] and the absence of information on exposure to risk factors in the general population makes confident aetiological attribution impossible in case series. Only two case control studies have reported from developing countries[14,15] and these have covered the full age range. These implicated family history and preceeding febrile seizures as risk factors. They did not examine other aetiological factors.

A Western study using a large birth cohort[16] has noted the contribution of CNS infection to epilepsy in children but de-emphasized perinatal factors. Studies from South Africa[9] and Nigeria[17] showing the important role of adverse obstetric events in the causation of epilepsy demonstrate the limited relevance to developing countries of studies performed in wealthy countries. Most studies of the cause of epilepsy have used a monofactorial aetiological model but it is likely that acquired brain insults interact with background factors that affect seizure threshold, such as genetic predisposition[18], to produce epilepsy in individuals and populations. There is good evidence that children in developing countries are exposed to higher rates of events that can cause epilepsy such as CNS infection[19,20] as well as an excess of antenatal and birth complications as indicated by perinatal mortality rates[21,22]. Studies of the aetiology of epilepsy have concentrated on events known to cause brain injury while neglecting

the background factors that may work with these insults to produce epilepsy. This paper reviews evidence that malnutrition may lower seizure threshold and contribute to the prevalence of epilepsy in children in developing countries.

Malnutrition, the electrolyte environment and epileptogenesis

Despite minor difference in the indices used, malnutrition in children under 5 years is highly prevalent in low income countries and declines with increasing prosperity to negligible levels in developed countries[23]. Its prevalence and effects in older children have received relatively little research attention.

Though broad syndromes of infant malnutrition have been described, local variations in dietary deficiency probably influence the spectrum of biochemical effects. Electrolyte disturbances have been identified in numerous series of young children admitted with protein energy malnutrition in developing countries. Dietary deficiency is rarely the sole cause of malnutrition in these cases; concomitant infections, particularly diarrhoea and gut parasitoses, further compromise nutrition by inducing malabsorbtion and the increased metabolic demands of attempting to mount an immune response.

These studies have reported reduced concentrations of albumin and plasma protein, hypokalaemia and hyponatraemia[24], hypomagnesaemia[25,26] and hypocalcaemia[27], the latter particularly associated with vitamin D deficiency. By the time hypomagnesaemia occurs tissue and CSF magnesium deficiency is usually severe because it is primarily an intracellular ion and neurological function is already adversely affected[26,28].

Studies of malnourished children have also shown that hypoglycaemia[29] is also a particular hazard of malnutrition in the presence of diarrhoea and may be due to failure of gluconeogenesis[30].

These reports generally represent the severer end of the spectrum of malnutrition; the extent to which these biochemical derangements occur in the majority of children suffering from chronic malnutrition of lesser severity is uncertain. The emphasis on younger children reflects their particular vulnerability but evidence for generalization of these findings up the age range comes from Antener *et al.*'s[27] study which included malnourished adults.

Many of the electrolyte abnormalities characteristic of severe malnutrition can lower seizure threshold. This can happen in hyponatraemia[31] and hypocalcaemia[32]. Seizures have also been observed in hypomagnesaemic malnourished children[25] that responded rapidly to administration of magnesium[33]. A high incidence of seizures has also been reported in hypoglycaemic children with diarrhoea and malnutrition[30] and induced hypoglycaemia has been shown to stimulate seizures in patients with underlying brain lesions[34].

Amino acids, malnutrition and epilepsy

A further line of enquiry concerns the effect of malnutrition on excitatory (Glutamate) and inhibitory (GABA) neurotransmitters. Reduced GABA levels have been found in the CSF[35] and in the cerebral cortex of patients with epilepsy[36], but not at the actual epileptic focus[37]. This would be compatible with GABA playing a role in preventing seizure spread rather than seizure genesis.

One possible mechanism whereby malnutrition could affect levels of inhibitory aminoacid neurotransmitters would be that low dietary intake of the amino acid or its precursors could lead to reduced availability in the brain.

In malnourished humans GABA levels have only been measured in the blood. The findings are contredictory, Smith *et al.*[38] found lowered levels, Agarwal *et al.*[39] found raised levels. The relationship between GABA levels in the blood, CSF, whole brain and at the synaptic cleft is especially relevant. When brain GABA is pharmacologically increased by administration of antiepilepsy drugs that prevent the breakdown of GABA, increases in CSF and blood GABA are subsequently observed[40]. Whether the process can occur in reverse, that is a change in blood GABA affecting CSF and brain levels of GABA, depends on transport across the blood brain barrier. Given the free exchange between CSF and the brain's extracellular space (which includes the synaptic cleft)[41] it is likely that CSF amino acid levels reflect those at the synaptic cleft. However, the relative impermeability of the blood brain barrier to GABA[42] as demonstrated by failure of CSF GABA to increase during intravenous infusion does not tell us whether CSF and brain GABA declines in the opposite condition of plasma depletion due to malnutrition.

A more convincing mechanism is suggested by Andrade and Paula-Barbosa[43]. They subjected rat pups to either 12 months of malnutrition on a low protein diet, or to a low protein diet for 6 months followed by a further 6 months of adequate diet, or to 12 months of adequate diet throughout. The rats entered the experiment at 2 months of age when postnatal brain growth would have been at a maximum. At the end of the experiment the density of GABAergic and cholinergic neurons in medial temporal lobe structures including the hippocampus was examined immunocytochemically. They found that GABAergic neurons in the hippocampus and dentate gyrus were depleted in the groups sub-

jected to malnutrition and showed no sign of recovery in the group that was switched to an adequate diet after 6 months. Though also depleted by malnutrition, the cholinergic neurons showed greater recovery after nutritional rehabilitation. Hippocampal damage plays a prominent role in partial epilepsy and if this finding applied to humans it would suggest that even a brief period of malnutrition in infancy could predispose to epilepsy later in life.

Lehmann and Hamberger's report that hypoglycaemia causes the release of glutamate in the hippocampus[44] offers an additional mechanism by which malnutrition lowers seizure threshold by increasing the level of an excitatory amino acid neurotransmitter.

Experimental and observational studies

The only experimental studies of the effect of malnutrition on seizure threshold have been conducted on rats. Stern *et al.*[45] demonstrated lowered seizure threshold in response to electroconvulsive shock in adult rats which had been reared on protein deficient diets. This finding did not fully reverse on reinstatement of a normal diet suggesting permanently altered brain function. Histological examination was not reported. Subsequently the same team[46], showed that the effect of malnutrition was specific for the method of seizure induction. They confirmed their previous findings on electroconvulsive shock, but were unable to demonstrate that it applied to kindled or pentylenetetrazol induced seizures.

Palencia *et al.*[47] fed a corn-based exclusion diet to weened rats in order to simulate the prevailing dietary deficiencies that affected the population in parts of Mexico. They then assessed the threshold for pentylenetetrazole-induced seizures and found it was significantly lower than in non-malnourished controls. Only a limited number of biochemical parameters were examined, but the malnourished rats had lower serum proteins, glucose and cholesterol. Electrolytes were not measured. Histological examination of the brains of the malnourished rats showed structural abnormalities consisting of atrophic neurones in the hippocampus, cerebellar and cerebral cortices. It is not clear whether chronic malnutrition-induced changes to the brain's microscopic structure were responsible for the lowered seizure threshold, or whether it was due to change in the biochemical environment. This is an important consideration because the former is probably irreversible whereas the latter should respond to nutritional rehabilitation.

Evidence in humans is equally scarce. Levav *et al.*[48] in Ecuador anthropometrically assessed nutrition, performed EEGs, examined stool for parasites and assessed iodine deficiency in 194 school-going children in a poor rural area. 6.6% of this malnourished sample had epileptiform EEG changes (spikes, sharp waves or paroxysmal features) which is a much higher proportion than the 1.6–2.7% that these researchers quoted from developed countries. Unfortunately they did not examine associations between measures of malnutrition, iodine deficiency and specifically epileptiform EEG changes. They did, however, demonstrate an association between iodine deficiency and any EEG abnormality.

Data also comes from a population-based epidemiological study of the prevalence of epilepsy in 8 to 12 year old children in Kerala, South India, in which every child was weighed and measured as well as asked questions to establish the presence of epilepsy[2]. Body mass index but not height was significantly lower in children with epilepsy compared to non-epileptic children from the same population. This association remained even when measures of social class were taken into account. The association with body mass index (wasting) rather than stature, implicates current rather than past malnutrition[49] suggesting that seizure threshold is lower in these children due to the acute metabolic effect of malnutrition[49]. Had it been due to structural changes due to nutritional brain insults at the time of maximum post-natal brain growth (and hence vulnerability) a deficit in height would have been expected, stunting being a measure of early malnutrition.

A cross-sectional study such as this cannot exclude social explanations for the association. Dike[50] in Zambia reported three infants with seizure disorders who were admitted with malnutrition for which no other cause could be found. He suggested that either subtle neurological disorders could impair a child's ability to feed or that they were the victims of 'conscious selective neglect'.

As well as potential mechanisms involving electrolyte disturbances or the effects of malnutrition on amino acid neurotransmitters outline above, a separate line of evidence comes from the observation that selenium deficiency can cause seizures in children[51,52]. Selenium deficiency is not purely a result of economic deprivation. Intake depends heavily on the content of the local soil making it a condition determined as much by geography as by poverty[53].

Finally, consideration has to be given to malnutrition and epilepsy being linked through reduced immunity. Numerous studies[54] have shown that malnutrition lowers resistance to infection; this could make malnourished children more vulnerable to a range of infections including neurotropic virus infections that cause epilepsy and are prevalent in developing countries.

This brief review has provided evidence that malnutrition could contribute to the raised prevalence of epilepsy in children in the developing world. Further

studies are needed to confirm the association but ethical as well as scientific considerations require the early conduct of intervention studies of nutritional rehabilitation in malnourished children with epilepsy.

REFERENCES

1. de Bittencourt, P. R. M., Adamolekum, B., Bharucha, N. *et al.* Epilepsy in the tropics: I. Epidemiology, socioeconomic risk factors and etiology. *Epilepsia* 1996; **37**: 1121–1127.
2. Hackett, R. J., Hackett, L. and Bhakta, P. The prevalence and associated factors of epilepsy in children in Calicut District, Kerala, India. *Acta Paediatrica* 1997; **86**: 1257–1260.
3. Rwiza, H. T., Kilonzo, G. P., Haule, J. *et al.* Prevalence and incidence of epilepsy in Ulanga, a rural Tanzanian district: a community based study. *Epilepsia* 1992; **33**: 1051–1056.
4. Durkin, M. S., Davidson, L. L., Hasan, Z. M. *et al.* Estimates of the prevalence of childhood seizure disorders in communities where professional resources are scarce: results from Bangladesh, Jamaica and Pakistan. *Paediatric and Perinatal Epidemiology* 1992; **6**: 166–180.
5. Matuja, W. B. P. Aetiological factors in Tanzanian epileptics. *East African Medical Journal* 1989; **66**: 343–348.
6. Aziz, H., Ali, S. M., Frances, P. *et al.* Epilepsy in Pakistan: A population-based epidemiologic study. *Epilepsia* 1994; **35**: 950–958.
7. Waruiru, C. M., Newton, C. R. J. C., Forster, D. *et al.* Epileptic seizures and malaria in Kenyan children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1996; **90**: 152–155.
8. Poneprasert, B. Japanese encephalitis in children in northern Thailand. *South-east Asian Journal of Tropical Medicine and Public Health* 1989; **20**: 599–603.
9. Leary, P. M. and Morris, S. Recurrent seizures in childhood; Western cape profile. *South African Medical Journal* 1988; **74**: 579–581.
10. Bern, C., Garcia, H. H., Evans, C. *et al.* Magnitude of the disease burden from neurocysticercosis in a developing country. *Clinical Infectious Diseases* 1999; **29**: 1203–1209.
11. Pal, D. K., Carpio, A. and Sander, J. W. Neurocysticercosis in developing countries. *Journal of Neurology, Neurosurgery and Psychiatry* 2000; **68**: 137–143.
12. Joshi, V., Katiyar, B. C., Mohan, P. K. *et al.* Profile of epilepsy in a developing country: A study of 1000 patients based on the international classification. *Epilepsia* 1977; **18**: 549–553.
13. Senanayake, N. and Roman, G. C. Epidemiology of epilepsy in developing countries. *World Health Organisation Bulletin* 1993; **71**: 247–258.
14. Gracia, F., Loo de Lao, S., Castillo, L. *et al.* Epidemiology of epilepsy in Guaymi Indians from Bocas del Toro province, Republic of Panama. *Epilepsia* 1990; **31**: 718–723.
15. Ogunniyi, A., Osuntokum, B. O., Bademosi, O. *et al.* Risk factors for epilepsy: case-control study in Nigerians. *Epilepsia* 1987; **28**: 280–285.
16. Nelson, K. B. and Ellenberg, J. H. Predisposing and causative factors in childhood epilepsy. *Epilepsia* 1987; **28** (Suppl. 1): 16–24.
17. Asindi, A. A., Antia-Obong, O. E., Ibia, E. O. *et al.* Neonatal seizures in Nigerian infants. *African Journal of Medicine and Medical Science* 1995; **24**: 243–248.
18. Schaumann, B. A. Family history of seizures in post-traumatic and alcohol associated seizure disorders. *Epilepsia* 1994; **35**: 48–52.
19. Gajana, A., Thenmozhi, V., Samuel, P. P. *et al.* A community-based study of subclinical flavivirus infections in children in an area of Tamil Nadu, India, where Japanese encephalitis is endemic. *Bulletin of the World Health Organisation* 1995; **73**: 237–244.
20. Bale, J. F. Viral encephalitis. *Medical Clinics of North America* 1993; **77**: 25–42.
21. Fikree, F. F. and Gray, R. H. Demographic survey of the level and determinants of perinatal mortality in Kararchi, Pakistan. *Paediatrics and Perinatal Epidemiology* 1996; **10**: 86–96.
22. Kunzel, W., Herrero, J., Onwuhafua, P. *et al.* Maternal and perinatal health in Mali, Togo and Nigeria. *European Journal of Obstetrics, Gynaecology and Reproductive Biology* 1996; **69**: 11–17.
23. World Bank. *World Development Report 1993: Investing in Health*. New York, USA, Oxford University Press.
24. Erinoso, H. O., Akinbami, F. O. and Akinyinka, O. O. Prognostic factors in severely malnourished hospitalised Nigerian children. *Tropical and Geographical Medicine* 1993; **45**: 290–293.
25. Caddell, J. L. Magnesium in protein-calorie malnutrition. *Journal of Pediatrics* 1965; **66**: 392–411.
26. Anonymous, Magnesium and Malnutrition. *The Lancet* 1967; **1**: 712–713.
27. Antener, I., Verwilghen, A. M., Van Geert, C. *et al.* Study of malnutrition III. Biochemical assessment of the dietary treatment and evolution of the illness. *Helvetica Paediatrica Acta* 1978; **33**: 543–562.
28. Leaver, D. D., Parkinson, G. B. and Schneider, K. M. Neurological consequences of magnesium deficiency: correlations with epilepsy. *Clinical and Experimental Pharmacology and Physiology* 1987; **14**: 361–370.
29. Wharton, B. Hypoglycaemia in children with kwashiorkor. *The Lancet* 1970; **i**: 171–173.
30. Bennish, M. L., Azad, A. K., Rahman, O. *et al.* Hypoglycemia during diarrhoea in childhood. *New England Journal of Medicine* 1990; **322**: 1357–1363.
31. Kumar, S. and Berl, T. Electrolyte quintet, Sodium. *The Lancet* 1998; **352**: 220–228.
32. Bushinsky, D. A. and Monk, R. D. Electrolyte quintet, calcium. *The Lancet* 1998; **352**: 306–311.
33. Back, E. H., Montgomery, R. D. and Ward, E. E. Neurological manifestations of magnesium deficiency in infantile gastroenteritis and malnutrition. *Archives of Diseases of Childhood* 1961; **37**: 106–109.
34. Sperling, M. R. Hypoglycemic activiation of focal abnormalities in the EEG of patients considered for temporal lobectomy. *Electroencephalography and Clinical Neurophysiology* 1984; **58**: 506–512.
35. Wood, J. H., Hare, T. A., Glaeser, B. S. *et al.* Low cerebrospinal fluid gamma aminobutyric acid content in seizure patients. *Neurology* 1979; **29**: 1203–1208.
36. Van Gelder, N. M., Sherwin, A. L. and Rasmussen, T. Amino acid content of epileptogenic human brain. *Brain Research* 1972; **40**: 385–393.
37. Perry, T. L., Hansen, S., Kennedy, J. *et al.* Amino acids in human epileptogenic foci. *Archives of Neurology* 1975; **32**: 752–754.
38. Smith, S. R., Pozefsky, T. and Chhetri, M. K. Nitrogen and amino acid metabolism in adults with protein-calorie malnutrition. *Metabolism* 1974; **23**: 603–618.
39. Agarwal, K. N., Bhatia, B. D., Batta, R. K. *et al.* Erythrocytic enzymes and amino acids related to glutamic acid metabolism in childhood hypoproteinemic states. *American Journal of Clinical Nutrition* 1981; **34**: 924–927.
40. Bohlen, P., Huot, S. and Palfreyman, M. G. The relationship between GABA concentration in the brain and cerebrospinal fluid. *Brain Research* 1979; **167**: 297–305.
41. Chapman, A. G. Amino acid abnormalities in plasma, CSF and brain in epilepsy. In: *Recent Advances in Epilepsy, No. 4* (Eds T. A. Pedley and B. S. Meldrum). London, Churchill Livingstone, 1988.

42. Davson, H., Welch, K. and Segal, M. B. *The Physiology and Pathophysiology of the Cerebrospinal Fluid*. Edinburgh, Churchill Livingstone, 1987.
43. Andrade, J. P. and Paula-Barbosa, M. M. Protein malnutrition alters the cholinergic and GABAergic systems of the hippocampal formation of the adult rat: an immunocytochemical study. *Neuroscience Letters* 1996; **211**: 211–215.
44. Lehmann, A. and Hamberger, A. Extracellular levels of amino acids in epilepsy: methods and findings. In: *Neurotransmitters and Epilepsy* (Eds R. S. Fisher and J. T. Coyle). New York, Wiley-Liss, 1991.
45. Stern, W. C., Forbes, W. B., Resnick, O. *et al.* Seizure susceptibility and brain amine levels following protein malnutrition during development in the rat. *Brain Research* 1974; **79**: 375–384.
46. Forbes, W. B., Stern, W. C., Tracy, C. A. *et al.* Effect of chronic protein malnutrition on experimentally induced seizures in the rat. *Experimental Neurology* 1978; **62**: 475–481.
47. Palencia, G., Calvillo, M. and Sotelo, J. Chronic malnutrition caused by a corn-based diet lowers the threshold for pentylenetetrazol-induced seizures in rats. *Epilepsia* 1996; **37**: 583–586.
48. Levav, M., Cruz, M. E. and Mirsky, A. F. EEG abnormalities, malnutrition, parasitism and goitre: a study of school children in Ecuador. *Acta Paediatrica* 1995; **84**: 197–202.
49. Waterlow, J. C. Current issues in nutritional assessment by anthropometry. In: *Malnutrition and Behaviour: Critical Assessment of Key Issues* (Eds J. Brozek and B. Schurch). Lausanne, Nestle Foundation, 1984: pp. 77–90.
50. Dike, G. L. Severe malnutrition due to subtle neurologic deficits and epilepsy: report of three cases. *East African Medical Journal* 1999; **76**: 597–598.
51. Weber, G. F., Maertens, P., Meng, X. *et al.* Glutathione peroxidase deficiency and childhood seizures. *The Lancet* 1991; **337**: 1443–1444.
52. Ramaekers, VTh., Calomme, M., Vanden Berghe, D. *et al.* Selenium deficiency triggering intractible seizures. *Neuropediatrics* 1994; **25**: 217–223.
53. Rayman, M. P. The importance of selenium to human health. *The Lancet* 2000; **356**: 233–241.
54. Chandra, R. K. Nutrition and the immune system: an introduction. *The American Journal of Clinical Nutrition* 1997; **66**: 460S–463S.