Chapter 21

SEIZURES

Seizures are a group of neurological disorders typified by muscle contractions, twitching and partial or complete loss of consciousness. Specific symptoms depend on the precise location in the brain of chaotic bursts of electrical activity. Seizures range from violent, uncontrollable contractions of the whole body to a subtle and momentary "loss of contact" that may appear to be little more than daydreaming.

Seizures have been referred to as convulsions, fits and epilepsy, as well as by other names that do not accurately reflect the various disorders. Types of seizures include tonic-clonic (gland mal), absence (perit mal), complex-partial (psychomotor, temporal lobe), focal (Jacksonian), and status epilepticus (intractable fits). Not all seizures are epileptic. The most common type of seizure in very young children are called febrile seizures, caused by the rapid onset of fever. Other causes of seizures include stroke or may be a result of injury, tumors, meningitis, hypoglycemia, alcohol withdrawal or other health complications.

Epilepsy – a specific type of seizure with recurrent, unprovoked attacks – is however the most common type, affecting close to three mullion North Americans – about one in a hundred people, half of them children or adolescents. Of these, one-half fortunately grows out of the disorder.

Treatment

Recurrent seizures usually require medication with such oral anticonvulsants as Phenobarbital, valproic acid, phenytoin and carbamazine. Patients may need to take these drugs indefinitely. Unfortunately they are not a cure and can have many side effects, some severe.

Nutritional supplements are used in both conventional and complementary medicine. B-vitamins, particularly B6 (pyridoxine), are effective against certain seizures. Magnesium is also useful, especially in seizures related to high blood pressure. Selenium is used in epileptics, since deficiency of this mineral may intensify the frequency and severity of seizures.

FREE RADICAL DAMAGE IN SEIZURES

Seizures are typified by tremendous bioelectrical activity in the affected area of the brain that generates free radicals in large numbers. Convulsions that provoke loss of consciousness may be accompanied by breathing abnormalities and subsequent oxidative stress. When frequent and/or prolonged, this oxidative stress can damage brain cells. May studies show that lipid peroxidation (a result of free radical formation) can lead to neuronal damage of destruction of these neurological cells. Moreover, the higher the level of oxidative stress in these tissues, the harder it is to treat. Patients respond less effectively to medication when the ongoing injury and nerve damage provokes further epileptic activity. Canadian researchers at the University of

Calgary have even suggested that this continual free radical damage may even result in certain brain tumors.

GLUTATHIONE LEVELS IN SEIZURES

Considerable research has demonstrated that glutathione levels fall significantly in seizure conditions. What is less clear is whether this glutathione deficiency causes seizures, results from them, or both. Nevertheless, the total body glutathione levels of seizure patients are measurable lower than those of normal individuals, and this GSH deficiency is even more noticeable in the affected areas of the brain.

Swiss scientists led by S.G. Mueller studied three groups: patients with active epilepsy, those with controlled epilepsy and non-epileptics. They determined that low glutathione levels more often lead to seizures than result from them. Other research supports this theory by showing how seizures are more frequent or severe when glutathione levels are experimentally lowered. Whatever the specific mechanism, the overall picture shows that glutathione levels fall lower and lower as seizures progress.

Worse still, not only are glutathione levels lowered by seizure activity, the drugs used to treat seizures themselves reduce glutathione levels even further. Japanese researchers H. Ono, A. Sakamoto and N. Sakura showed that both cabamazepine and phenytoin-popular anti-seizure medications-diminish glutathione and leave cells even more susceptible to oxidative damage. Turkish physiologists found the same of valproic acid, another anti-seizure drug. However, scientists studying childhood seizures at Harvard University found that glutathione levels improved after anticonvulsants were halted and patients were given selenium.

GLUTATHIONE PROTECTS FROM SEIZURES

Since glutathione directly affects the activity of brain cells, it is called neuromodulator, Japanese scientists K. Abe, K. Nakanishi and H. Saito protected animals from drug-induced seizures by injecting glutathione directly into the fluid of the brain and spinal cord. Canadians at Toronto Western Hospital showed that combined vitamin E and glutathione reduced the number of brain cells damaged after seizure activity. In Texas S.G. Jenkinson, J.M. Jordan and C.A. Duncan were able to protect laboratory animals from seizures and death by injecting them with glutathione and Italians at the University of Milan successfully prevented seizures caused by isoniazid-a tuberculosis medication-by administering patients with glutathione beforehand.

Several scientists have used n-acetylcysteine (NAC, see chapter 4), a powerful glutathione precursor, to treat seizures, and Swedish researchers led by E. Ben-Manachem applied it to patients suffering from progressive myoclonic epilepsy-a particularly hard to treat disease that gradually destroys the nervous system. Patients given a daily dose of 6 grams showed marked improvements, and an American team from Gainesville, Florida used NAC, vitamin E, B2, zinc and selenium to treat this type of seizure, obtaining similar improvements.

CONCLUSION

Free radical formation and oxidative stress can be seen as both a cause and a result of seizures, and conditions that diminish glutathione levels-including the use of anti-seizure drugs themselves-may well lower glutathione levels as well. Since glutathione is also itself an anticonvulsant, it may be used as a complementary therapy to both treat and prevent seizures as well as to lessen the adverse effects of conventional drugs.

REFERENCES IN CHAPTER 21
SEIZURES

Abbott LC, Nejad HH, Bottje WG, Hassan AS, Glutathione levels in specific brain regions of genetically epileptic (tg/tg) mine, *Brain Res Bull 1990 Oct;25(4):629-31*

Abe K, Nakanishi K, Saito H, The anticonvulsive effect of glutathione in mice, *Biol Pharm Bull 1999 Nov;22(11):1177-9*

Abe K, Nakanishi K, Saito H, The possible role of endogenous glutathione as an anticonvulsant in mice, *Brain Res 2000 Jan;31;854(1-2):235-8*

Belissimo MI, Amado D, Abdalla DSm Ferreira EC, Cavalheiro EA, Naffah-Mazzacoratti MG, Superoxide dismutase, glutathione peroxidase activities and the hydro peroxide concentration are modified in the hippocampus of epileptic rats, *Epilepsy es 2001 Aug;46(2):121-8*

Ben-Menachem E, Kyllerman M, Marklund S, Superoxide dismutase and glutathione peroxidase function in progressive myoclonus epilepsies, *Epilepsy Res 2000 Jun;40(1):33-9*

Beutler E, Curnette JT, Forman L, Glutathione peroxidase deficiency and childhood seizures, *Lancet 1991 Sep 14;338(8768):700*

Cengiz Mm Yuksei, A, Seven M, The effects of carbamazepine and valproic acid on the erythrocyte glutathione, glutathione peroxidase, superoxide dismutase and serum lipid peroxidation in epileptic children, *Pharmacol Res 2000 Apr;41(4):423-5*

Cock HR, Tong X, Hargreaves IP, Heales SJ, Clark JB, Patsalos PN, Thos M, Groves M, Schapira AH, Shorvon DS, Walker MC, Mito-chondrial dysfunction associated with neuronal death following status epilepticus in rat, *Epilepsy Res 2002 Feb;48(3):157-68*

Erakovic V, Zupan G, Varljen J, Radosevic S, Simonic A, Electroconvulsive shock in rats: changes in superoxide dismutase and glutathione peroxidase activity, *Brain Res Mol Brain Res 2000 Mar 29;76(2);266-74*

Frantseva MV, Perez Valazquez JL, Tsoraklidis G, Mendonca AJ, Adamchik Y, Mills LR, Carlen PL, Burnham MW, Oxidative stress is involved in seizure-induced neurodegeneration in the kindling model of epilepsy, *Neuroscience 2000;97(3):431-5*

Frantseva MV, Velazquez JL, Hwant PA, Carlen PL, Free radical production correlates with cell death in an in vitro model of epilepsy, *Eur J Neurosci 2000 Apr;12(4):1431-9*

Gluck MR, Jayatilleke E, Show S, Rown AJ, Haroutunian V, CNS oxidative stress associated with the kainic acid rodent model of experimental epilepsy, *Epilepsy Res 2000 Mar;39(1):63-71*

Hiramatsu M, Mori A, Brain glutathione and seizures, *Folia Psychiatr Neurol Jpn 1980;34(3):363*

Hiramatsu M, Mori A, Reduced and oxidized glutathione in brain and convulsions, *Neurochem Res 1981 Mar;6(3):301-6*

Hurd RW, Wilder BJ, Helveston WR, Uthman BM, Treatment of four siblings with progressive myoclonus epilepsy of the Unverricht-Lundborg type with N-acetylcysteine, *Neurology 1996 Nov; 47(5):1264-8*

Jenkinson SG, Jordan JN, Duncan CA, Effects of selenium deficiency on glutathione-induced protection from hyperbaric hyperoxia in rat, *AM J Physiol 1989 Dec;257(6 Pt 1):L393-8*

Jiang D, Akopian G, Ho YS, Walsh JP, Andersen JK, Chronic brain oxidation in glutathione peroxidase knockout mouse model results in increased resistance to induced epileptic seizures, *Exp Neurol 2000 Aug;164(2):257-68*

Kurekci AE, Alpay F, Tann\indi S, Gorcay E, Ozcan O, Akin R, Isimer A, Sayai A, Plasma trace element, plasma glutathione peroxidase, and superoxide dismutase levels in epileptic children receiving ant epileptic drug therapy, *Epilepsia 1995 Jun;36(6):600-4*

Liu CS, Wu HM, Koa SH, Serum trace elements, glutathione, copper/zinc superoxide dismutase, and lipid peroxidation in epileptic patients with phenytoin or carbamazepine monotherapy, *Clin Neuropharmacol 1998 jan-Feb;21(1):62-4*

Lores Arnaiz S, Travacio M, Llesuv S, Rodriguez De Lores Arnaiz G, Regional vulnerability to oxidative stress in a model of experimental epilepsy, *Neurochem Res 1998 Dec;23(12):1477-83*

Louw DF, Bose R, Sima AA, Sutherland GR, Evidence for a high free radical state in low-grade astrocytomas, *Neurosurgery 1997 Nov;41(5):1146-50; discussion 1151*

Mueller SG, Trabesinger AH, Boesiger P, Wieser HG, Brain glutathione levels in patients with epilepsy measured by in vivo (1)HMRS, *Neurobiology 2001 Ict 23l57(8)L1422-7*

Ogita K, Kitayama T, Okuda H, Yoneda Y, Effects of glutathione depletion by 2-cyclohexen-1-one on excitatory amino acids-induced enhancement of activator protein-1 DNA binding in murine hippocampus, *J Neurochem 2001 Mar;76(6):1905-15*

Ono H, Sakamoto A, Sakura N, Plasma total glutathione concentrations in epileptic patients taking anticonvulsants, *Clin Chim Acta 2000 Aug;298(1-2):135-43*

Peacock MD, Schekn DA, Lawrence RA, Morgan JA, Jenkinson SG, Elimination of glutathione-induced protection from hyperbaric hyperoxia by acivicin, J *Appl Physiol 1994 Mar;76(3):1279-84*

Pinelli, A, Trivulzio S, Colombo-Zefinetti G, Tofanetti O, Anti-convulsant effects by reduced glutathione and related amino acids in rats treated with isoniazid, *Toxicology 1988 Jan;48(1):103-7*

Ramaekers VT, Calomme M, Vanden Berghe D, Makropoulos W, Selenium deficiency triggering intractable seizures, *Neuropediatrics 1994 Aug;25(4):217-23*

Ravikumar A, Arun P, Devi KV, Augustine J, Kurup PA, Isoprenoid pathway and free radical generation and damage in neuropsychiatric disorders, *Indian J Exp Biol 2000 May;38(5):438-46*

Santavuori P, Heiskala H, Westermarck T, Sainio K, Moren R, Experience over 17 years with antioxidant treatment in Spielmeyer-Sjogren disease, *Am J Med Genet suppl 1988;(5):265-74*

Singh R, Pathak DN, Lipid peroxidation and glutathione peroxidase, glutathione reductase, superoxide dismutase, catalse, and glucose-6-phosphate dehydrogenase activities in FeCl3-induced epileptogenic foci in the rat brain. *Epilepsia 1990 Jan-Feb;31(1):15-26*

Sudha IR, Rao AV, Rao A, Oxidative stress and antioxidants in epilepsy, *Clin Chim Acta 2001 Jan;30(1-2):19-24*

Tupeev IR, Kryzhanovskii GN, Nikushkin EV, Bordiukov MM, Iuzefova SM, The antioxidant system in the dynamic combined treatment of epilepsy patients with traditional anticonvulsant preparations and an antioxidant-alpha-tocopherol, *Biull Eksp Biol Med 1993 Oct;116(10):362-4*

Weber GF, Maertens P, Meng XZ, Pippenger CE, Glutathione peroxidase deficiency and childhood seizures, *Lances 1991 Jun 15;337(8755):1443-4*

Wei YH, Lu Cy, Wes Cy, Ma YS, Lee Hc, Oxidative stress in human aging and mitochondrial respiration and impaired antioxidant enzyme systems, *Chin J Physiol 2001 Mar 31;44(1):1-11*

Yuksei A, Cengiz M, Seven M, Ulutin T, Erythrocyte glutathione, glutathione peroxidase, superoxide dismutase and serum lipid peroxidation in epileptic children with valproate and carbamazepine monotherapy, *J Basic Clin Physiol Pharmacol 2001;11(1):73-81*

Yuksei A, Cengiz M, Seven M, Ulutin T, Changes in the antioxidant system in epileptic children receiving antiepileptic drugs; two-year prospective studies, *J Child Neurol 2002 Aug;16(8):603-6*