LETTERS

Organophosphate poisoning case with atypical clinical survey and magnetic resonance imaging findings

Organophosphorous compounds, the anticholinesterases produce significant morbidity and mortality. Although exact estimates are not available, hospital based statistics suggest that nearly half of the admissions to emergency with acute poisoning are attributable to organophosphates.[1] Sahin *et al* reported an organophosphate poisoning proportion of 15.1% among 564 poisonings.[2] Patients with organic insecticide poisoning present with a spectrum of manifestations ranging from gastrointestinal symptoms of nausea, vomiting, and diarrhoea to severe neurological manifestations of fasciculations, seizures, and neuromuscular weakness and paralysis or cardiac manifestations of arrhythmias and conduction disturbances.[3] The overall mortality was reported as 18%.[4]

We report a case with atypical neurological findings and magnetic resonance imaging (MRI) lesions attributable to organophosphate poisoning.

A previously healthy 31 year old man from Denizli (Turkey) presented with sudden onset of nausea, vomiting, and loss of conscious. During four days before the onset of his symptoms he was more irritable than usual. Five hours before his admission nausea and vomiting had begun after he ate royal jelly and he lost his conscious progressively.

He was sterile and he was informed of the diagnosis of asospermia on the day when he was intoxicated. His family history was unremarkable.

While he was admitted to the intensive care unit he was unconscious, his blood pressure was measured at 110/70 mm Hg, and heart rate was 62/minute. His body temparature was 39℃. His eyes were open but he was not looking meaningful. He was in a decerebrate posture. His pupils were bilaterally myotic and his left eye was deviated to interior and down at primary position. Babinsky sign was bilaterally positive. Deep tendon reflexes were overactive at his lower extremities. Tracheal secretion was increased.

Laboratory studies were unremarkable except for white blood cell of 20 900 K/µl. Pseudocholinesterase activity was 1860 (normal range: 3500–8500) on the first day, 890 on the second day, and 860 on the third day. CSF examination was normal. Blood and urine toxicological investigation showed that he was intoxicated with thyiometane and fenpropothine (insecticides) and also a high concentration of paracetamol was found in his gastric fluid examination. His cranial computed tomography scan showed a subarachnoid cyst at the posterior fossa and there was no pathological contrast enhancing. MRI showed hyperintense lesions at T2W images at the level of mesencephalone and cerebellum. On the third day, a second MRI showed that the mesencephalic and cerebellar lesions were enlarged (fig 1).

As we could not exclude the diagnosis of herpes encephalitis, he was given antiviral therapy. He was also treated with the antidotes atropine and pralidoxime, decreasing consciousness necessitated intubation, mechanical ventilation, and other supportive measures but his clinical progression worsened and he died after a severe ventricular arrhythmia resulting with cardiac arrest.

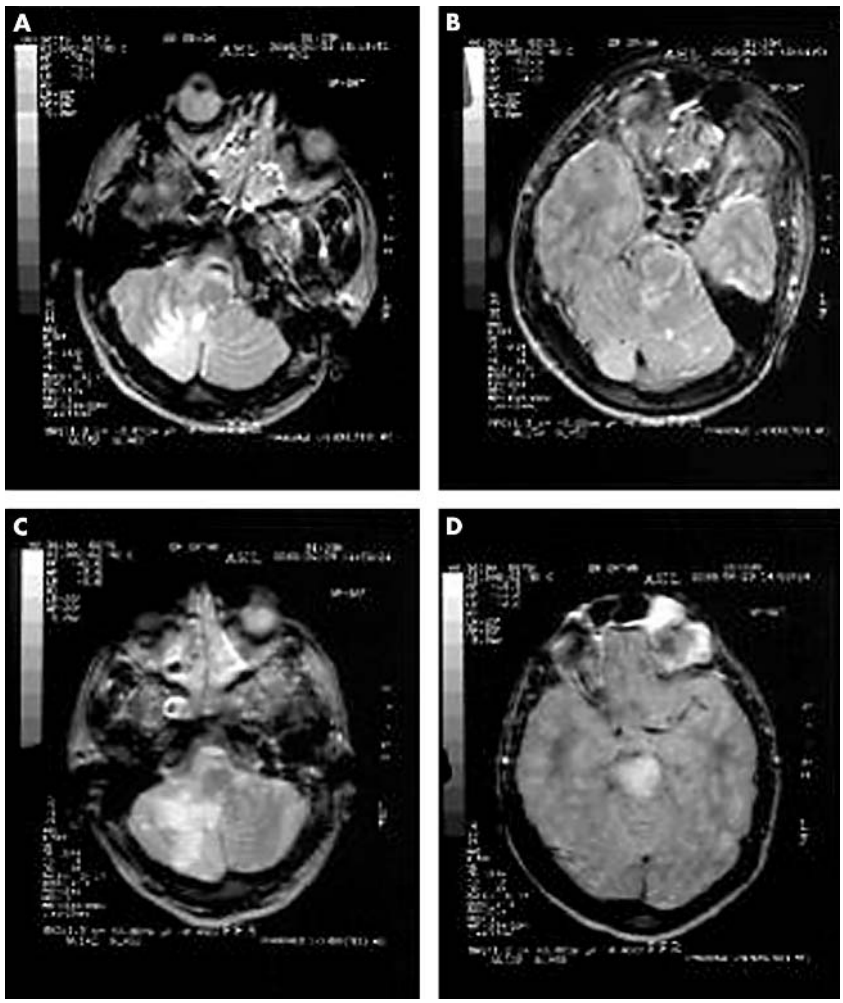

Figure 1 (A) First MRI T2W image, cerebellum; (B) first MRI T2W image, mesencephalon; (C) second MRI T2W image, cerebellum; (D) second MRI T2W image, mesencephalon.

Comment

The acute muscarinic and nicotinic side effects of organophosphate poisoning are well known. After accidental or suicidal exposure, anticholinesterases lead to three well defined neurological syndromes—that is, initial life threatening acute cholinergic crisis, which often requires management in intensive care unit, intermediate syndrome in which cranial nerve palsies, proximal muscle weakness, and respiratory muscle weakness are common and patients often require respiratory support, and delayed organophosphate induced polyneuropathy.[1]

Our patient did not show these well defined neurological syndromes. However, decerebrate posture and eye deviation indicated a broad brain stem lesion. In the first hours he was not unconscious and obeying orders occasionally. Normal EEG findings supported that there was not a serious cortical involvement. This is a rare clinical status and only Hollis *et al* have reported two cases of organophosphate poisoning misdiagnosed as having brain stem stroke.[5]

Yilmazlar *et al* reported perfusion defects in brain single photon emission computed tomography particularly in the parietal lobe of patients with organophosphate poisoning[6] and Wang *et al* reported that photon emission computed tomography analysis may be helpful in estimating the metabolic deficit of visual cortex and in establishing the organic nature of cortical visual loss in acute organophosphorous poisoning cases.[7] However, well localising MRI findings attributable to organophosphate poisoning have not been previously reported.

Hyperintense lesions in T2W images may be seen in viral encephalitis and other subacute brain stem infections but this was not the case because toxic agents had been fixed and clinical findings worsened despite antiviral therapy. Another clue for organophosphate intoxication of the patient was typical reversible cholinergic signs with atropine administration such as improving bradycardia.

We report on this patient because of atypical clinical survey, MRI findings, and well localised lesion at the early period of toxication.

E Teke
Neurology Department, Pamukkale University, Denizli, Turkey

H Sungurtekin
Aneastesiology and Reanimation Department, Pamukkale University

T Sahiner
Neurology Department, Pamukkale University

H Atalay
Aneastesiology and Reanimation Department, Pamukkale University

S Gur
Neurology Department, Pamukkale University

Correspondence to: Dr E Teke, Pamukkale University, Medicine Faculty, Neurology Department, 20100 Denizli, Turkey; eylemteke@yahoo.com

doi: 10.1136/jnnp.2003.022830

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Coincidence of a large SCA12 repeat allele with a case of Creutzfeld-Jacob disease

The spinocerebellar ataxias (SCAs) are a group of autosomal dominant inherited neurodegenerative disorders characterised by progressive cerebellar dysfunction. Besides cerebellar manifestations a variety of associated neurological signs, such as ophthalmoplegia, dementia, or pyramidal and extrapyramidal signs may occur. At least 21 loci for SCAs including 11 different genes have been identified. SCA 1, 2, 3, 6, 7, and 17 are caused by expansion of a translated CAG repeat in the corresponding gene leading to an expanded polyglutamine tract in the translated protein. In contrast, Holmes and colleagues[1] recently described a large pedigree with a new form of autosomal dominant ataxia (SCA12) associated with an expanded CAG tract in the 5′ untranslated region of the gene PPP2R2B, encoding a brain specific regulatory subunit of protein phosphatase PP2A. Clinical findings in SCA12 patients include upper extremity tremor, cerebellar signs and late onset dementia.[2]

We report on a patient with Creutzfeld-Jakob disease (CJD) carrying a 49 CAG repeat at the SCA12 locus. Additionally, we analysed a large sample of sporadic and hereditary ataxia patients for SCA12 mutations.

A 57 year old man of German origin presented subacutely with gait ataxia and a striking action tremor. Shortly after disease onset, his wife also noticed dysarthria. There was no evidence for neurological diseases in his family. His father died at 43 years from cardiac infarction, his 80 year old mother has no other children. On neurological examination, he showed no signs of cognitive impairment, oculomotor performance was normal. Deep tendon reflexes were depressed, there were no paresis, no pathological signs, and sensory testing was normal for pain, temperature, and touch. His gait was severely ataxic, there was a moderate dysmetria of the upper and lower limbs with a prominent action tremor.

An initial brain MRI was normal. Extensive blood tests including vitamins B12 and E, paraneoplastic antibodies and serum ceruloplasmin showed no pathological results. His cerebrospinal fluid was normal, except for a moderately raised protein level.

Electrophysiology showed subclinical sensory motor neuropathy. A genetic analysis of SCAs revealed a repeat expansion of 49 CAGs in the PPP2R2B gene for SCA12.

The disease rapidly progressed and after four months the patient additionally developed dementia with disorientation and paranoid hallucinations together with a deterioration of his neurological status especially for the ability to coordinate his movements. A second MRI scan now showed bilateral signal hyperintensity in the putamen and caudate nucleus, as well as the frontal, parietal, and insular cortices. EEG showed slowing of background activity with bursts of generalised θ rhythm. Additionally, CSF was positive for 14.3.3 protein leading to the assumption of a probable CJD case.

The patient died two months later because of aspiration pneumonia. Necropsy revealed a brain of 1265 g, which appeared to be unaffected macroscopically. Histological investigations showed moderate to severe spongiform changes with confluent vacuoles, a mild to moderate astrocytic gliosis, and a moderate nerve cell loss in the cerebral neocortex and, to a variable extent, in the basal ganglia, thalamic nuclei, and midbrain structures. The hippocampal formation and brain stem nuclei were comparatively free of pathological changes. Spongiform changes were seen also in the molecular layer of the cerebellum together with a granule cell loss. Kuru plaques could be detected next to Purkinje cells as a hallmark of this special subtype of CJD.[3] With a monoclonal antibody against prion protein (Gö138), perivacuolar prion protein deposits were detectable in cortical areas and plaque-like or granular deposits in the cerebellum. Genetic analysis of the PRNP gene revealed the MV genotype at codon 129.

Additionally, we screened 1028 patients from northern Germany with cerebellar ataxia, including 113 patients with positive family history, and 150 healthy controls for SCA12 mutation.

Repeat expansions in all other known SCA genes had been previously excluded.

SCA12 expansions larger than 50 repeats were not detected in any of the patients or controls. In addition to the CJD patient with 49 CAG repeats, alleles of 40 respectively 41 repeats were found in two patients with late onset sporadic ataxia. All other allele sizes ranged from 4 to 28 CAG repeats with a heterozygosity of 60.7% as shown in table 1. The most common allele containing 10 CAG repeats was found in 61.7% of all chromosomes.

Comment

SCA12 is a very rare entity for autosomal dominant and sporadic ataxias with only six Indian and one American pedigree of German descent published at present.[2 4 5] The expanded alleles ranged from 55 to 78 CAG repeats, whereas normal alleles ranged from 7–31 repeats. Recently, an allele of even 45 repeats was described in an Indian control subject without any neurological symptoms and with no family history of ataxia.[5] We now present a case of CJD bearing a repeat of 49 CAG copies. The initial symptoms of this patient resembled those described in SCA12 patients. In particular the action tremor in combination with cerebellar signs that preceded the cognitive impairment for four

Table 1 Distribution of alleles at the SCA12 locus among 1029 ataxia patients and 150 healthy controls. Undetected repeat lengths are not shown

	Healthy controls		Ataxia patients	
$(CAG)_n$	Number	Frequency (%)	Number	Frequency (%)
4	–	–	2	0.10
7	1	0.33	1	0.05
9	2	0.67	49	2.38
10	176	58.67	1270	61.71
11	3	1.00	20	0.97
12	1	0.33	3	0.15
13	34	11.33	229	11.13
14	33	11.00	174	8.45
15	37	12.33	244	11.86
16	1	0.33	20	0.97
17	4	1.33	19	0.92
18	–	–	14	0.68
19	1	0.33	2	0.10
20	1	0.33	2	0.10
21	5	1.67	–	–
22	–	–	1	0.05
23	–	–	1	0.05
24	1	0.33	1	0.05
26	–	–	1	0.05
28	–	–	2	0.10
40	–	–	1	0.05
41	–	–	1	0.05
49	–	–	1	0.05

months was striking. On the other hand, ataxia is also a prominent clinical feature of the Kuru-plaque variant found in this patient, which is linked to the MV genotype at codon 129 and PRP^{sc} type 2. However, we cannot elucidate whether CJD of this patient unmasked SCA12 at a subclinical stage or whether the 49 allele is a large and rare normal allele without any influence on the phenotype and, unfortunately, there are no other family members available for genetic evaluation. What remains is the coincidence of two very rare diseases, respectively genetic variations. The protein phophatase PP2A may play a part in tau phosphorylation and apoptosis. Therefore, the possibility that a large SCA12 repeat could influence the pathogenesis of sporadic CJD, especially the Kuru-plaques variant, should be further evaluated.

The role of the 40 and 41 CAG repeats in two sporadic late onset ataxia cases is also difficult to interpret and we cannot exclude a pathogenic influence, although an even larger allele was found in a young Indian healthy control. The findings of this study implicate a more sophisticated interpretation of SCA12 alleles and raise the question about the diagnostic threshold between normal and expanded alleles.

Y Hellenbroich
Institute of Human Genetics, University of Lübeck, Germany

W Schulz-Schaeffer
Department of Neuropathology, University of Göttingen, Germany

Y Hellenbroich, M F Nitschke
Department of Neurology, University of Lübeck

J Köhnke
Institute of Human Genetics, University of Lübeck

G Händler
Department of Radiology, University of Lübeck

K Bürk
Department of Neurology, University of Tübingen, Germany

E Schwinger, C Zühlke
Institute of Human Genetics, University of Lübeck

Correspondence to: Dr Y Hellenbroich, Institute of Human Genetics, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany; hellenbroich@gmx.de

doi: 10.1136/jnnp.2003.028381

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Pre-treatment with corticosteroids and a single cycle of high dose albendazole for subarachnoidal cysticercosis

Cysticercosis is a common parasitic disease of the central nervous system and a pleomorphic neurological disorder. It is an endemic problem in developing countries and is now increasing in industrialised nations.[1] In Mexico neurocysticercosis is one of the main reasons for neurological consultation, and the first cause of epilepsy in adults.[2] The treatment of neurocysticercosis is controversial and depends on the clinical and neuroimaging features, as well as the extent and severity of the associated inflammatory reaction.[3] Basal subarachnoidal cysticercosis and racemose disease of sylvian fissure may behave aggressively producing intracranial hypertension, obstructive hydrocephalus, chronic arachnoiditis, vasculitis, and cerebral infarctions.[4] Subarachnoidal cysticercosis may have a chronic course and a poor prognosis, and is still treated surgically. In a recent open trial of 33 patients with subarachnoidal cysts of at least 50 mm in diameter, treatment with albendazole at a dose of 15 mg/kg/day during 28 days produced an adequate response in 12 patients (36%). The remaining 21 patients (64%) required repeated courses of albendazole and 10 treatments with praziquantel because of a partial or incomplete response to the first albendazole cycle.[5] Repeated treatments are not a minor problem in areas where cysticercosis is endemic and medical resources are limited. To explore a more effective regimen for subarachnoidal cysticercosis we started a pilot study in 1998 with corticosteroids pretreatment and a single course of a higher albendazole dose.

We included 12 patients with the diagnosis of subarachnoidal cysticercosis based in clinical data, imaging studies, and inflammatory cerebrospinal fluid with a positive enzyme linked immunosorbent assay (ELISA) test against cysticercal antigens. After written informed consent six hospitalised patients were pre-treated with intravenous dexamethasone at a dose of 8 mg every eight hours for five days. Four outpatients not receiving corticosteroids were given oral prednisone at dose of 1.5 mg/kg of body weight per day for five days. Two patients with severe arachnoiditis with incomplete response to prednisone, one of them with vasculitis proved by angiography were already receiving cyclophosphamide 100 mg per day, the drug was continued in both and one of them was also pre-treated with oral prednisone as above.

Albendazole was given at a dose of 30 mg/kg of body weight per day in three divided doses for 15 days. As soon as oral intake was tolerated patients taking dexamethasone were switched to prednisone at dose of 1 mg/kg of body weight a day. After four weeks, and depending on the clinical status prednisone dose was tapered individually. Magnetic resonance imaging (MRI) was performed before treatment and three to six months after treatment.

Four men and eight women with an average age of 32.8 years (range 20 to 47) were included. The mean hospital stay for inpatients was 17 days. Table 1 gives symptoms and signs before treatment and at the end of the 15 days of albendazole treatment. In five patients a ventriculoperitoneal shunt was placed before albendazole treatment. In seven patients, corticosteroids improved clinical manifestations within the first 24 hours.

On baseline MRI, the number of subarachnoid cysts varied from 1 to 24 cysts per patient; 10 patients had cysts in the basal cisterns and three had racemose cysts in Sylvian fissure. In three patients additional lobar and subcortical cysts were also present and ependymal or leptomeningeal enhancement was observed in five patients.

On MRI studies at six months of follow up a reduction of 86% of the number of the subarachnoidal vesicles was observed, decreasing from 73 to 10 cysts ($p = 0.02$; Mann-Whitney U test two tailed), with a

Table 1 Changes after treatment in neurological symptoms, signs, and cerebrospinal fluid (CSF) analysis

	Before treatment	After 15 days of corticosteroids and albendazole treatment	
Symptoms	**Number**	**Number**	**p Value***
Headache	11	7	0.115
Nausea	8	2	0.036
Vomiting	7	1	0.027
Blurred vision	3	1	0.590
Somnolence	3	0	0.217
Abnormal mental status	3	1	0.590
Seizures	3	1	0.590
Diplopia	3	0	0.478
Signs			
Intracranial hypertension	11	2	0.001
Papilloedema	10	3	0.012
Abnormal ocular movements	3	0	0.217
Incoordination	2	1	1.000
Motor deficit	1	0	1.000
CSF	**Before treatment**	**At six month follow up**	
Opening pressure mean (SD)	236 (130)	159 (37)	0.018†
Glucose mean (SD)	62 (39)	45 (15)	0.119†
Proteins mean (SD)	73 (94)	97 (117)	0.564†
Cells mean (SD)	70 (133)	59 (110)	0.998†
ELISA+cysticercus antigens	9	12	0.590

*Univariate analysis by Fisher's exact test. †Mann-Whitney U test, two tailed.

volume reduction of 80%. Eight patients had satisfactory clinical recovery and four patients presented minor neurological deficit with functional independence.

During treatment one patient required ventriculoperitoneal shunt revision for acute intracranial hypertension. In the remaining patients the observed adverse effects were headache and nausea in two who did not required drug withdrawal.

Significant changes after treatment were observed mainly in symptoms and signs of intracranial hypertension and these were attributable to corticosteroid effects or shunting, or both. No significant modifications of glucose cells and protein levels of CSF were observed during six months of follow up. This means that chronic aracnoiditis continues after cyst destruction, and for some patients corticosteroids are necessary for long term treatment. We base our dose reductions according to clinical parameters, CSF characteristics, and leptomeningeal enhancement (MRI). In this study ELISA test's sensitivity increased after treatment.

Pre-treatment with corticosteroids reduces the risk of complications secondary to destruction of cysticerci.[4–5] In our patients an immediate clinical improvement seemed to be an indicator of adequate tolerance to subsequent albendazole treatment. Because of the variability of albendazole pharmacokinetics, we considered that treatment with 30 mg/kg/day of albendazole will increase its concentration in plasma and CSF, improving the efficacy. This small series shows that a higher albendazole dose along with corticosteroid treatment was safe and useful in the treatment of subarachnoidal cysticercosis. Patients need to be carefully selected and require close observation and to be available for long term follow up. A randomised trial of standard compared with high albendazole dose is in progress at our centre.

C Márquez-Caraveo, F Góngora-Rivera, J Santos Zambrano, R Hernández, J L Soto-Hernández

Department of Neurology, Infectious Disease and Emergency Room of the National Institute of Neurology and Neurosurgery Manuel Velasco Suarez, Mexico City, Mexico

Correspondence to: Dr J L Soto-Hernández, Department of Infectious Disease, National Institute of Neurology and Neurosurgery Manuel Velasco Suárez, Insurgentes Sur 3877, La Fama, Tlalpan, CP 14269, Mexico, DF; sotohe51@prodigy.net.mx

doi: 10.1136/jnnp.2003.023572

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Short term benefit of battery depletion in vagus nerve stimulation for epilepsy

Interest in neurostimulation to treat epilepsy has rekindled over the past decade, with vagus nerve stimulation (VNS) now an accepted part of the algorithm for care of patients with medically refractory epilepsy.[1] More than 15 000 VNS devices have been surgically implanted in patients around the world. The reported improvements in seizure control are modest and the mechanism by which VNS may exert its effects is unclear, however, the benefits are presumed to be directly related somehow to the electrical stimulation applied to the nerve. A small number of relevant experimental studies have shown antiepileptic effects related to VNS, although the effects may be non-specific, for example, in rats heating of the tail is equally effective as stimulation of the vagus nerve in stopping seizures and decreasing interictal spikes.[2] In our own work with thalamic deep brain stimulation for epilepsy we found that the observed benefits in patients' seizure control bore no relation to whether the stimulators were actually turned on or not.[3] Because patients can sense active VNS in the form of laryngeal side effects, no similar sham stimulation placebo has been possible with VNS.

If stimulation of the vagus nerve is actually a necessary part of VNS for epilepsy, depletion of the stimulator battery would be expected to result in an increase in seizures. Indeed, status epilepticus was recently reported to have occurred in one patient after stopping VNS for an elective brain MRI scan.[4]

No study has been formally published describing the effects of battery depletion in a large group of patients treated with VNS for epilepsy, however, the data from just such a study have been published informally—in the Cyberonics *VNS Physician's Manual*.[5] It is of interest to examine these data. Over the course of follow up of patients in the E03 VNS trial,[6] a total of 72 battery depletions in 68 patients occurred. Seizure frequency after battery depletion was monitored for one to four weeks after stimulation was stopped, with the outcome results divided into three groups: patients having a greater than 25% increase in seizures, patients unchanged with a less than 25% increase or decrease in seizures, and patients with a greater than 25% decrease in seizures. Forty two of 72 cases (58%) were in the last group—that is, the large majority of patients *improved* after battery depletion. Nineteen of 72 cases (26%) were unchanged and 11 of 72 (15%) worsened.

A χ^2 analysis of the results comparing patients with a greater than 25% seizure reduction with patients with a greater than 25% increase in seizures after battery depletion shows a highly significant benefit to battery failure ($p<0.0001$; $\chi^2 = 18.14$, two tailed test). This is the most significant finding of any statistical analysis performed in all of the VNS studies used to support licensing of the device as a treatment for epilepsy.[5–7] As the research hypothesis here specifies the direction in which a change will occur—that is, "there will be an increase in seizures when VNS stops," the alternative hypothesis is actually one tailed, which makes the significance of the findings even greater ($p<0.00005$). This means that the probability that the observed findings of improvement with battery depletion in most patients could have occurred by chance is less than 1 in 20 000. It is possible that the findings do represent such a chance occurrence. It is equally possible, or perhaps more probable, that any sort of non-specific change in patients with epilepsy might provide a perturbation sufficient to effect improvements in seizure control, at least in the short term. Either way, benefits in seizure control with VNS in humans seem to have little specific to do with active stimulation of the vagus nerve.

R Wennberg

Krembil Neuroscience Centre, Toronto Western Hospital, University of Toronto, 399 Bathurst Street, 5W444, Toronto, ON Canada M5T 2S8; r.wennberg@utoronto.ca

doi: 10.1136/jnnp.2003.028050

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