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Sleep Attacks and the New Dopamine Agonists: Should Pramipexole and Ropinirole Be Used in Patients Who Drive?

ABSTRACT & COMMENTARY

Source: Frucht S, et al. *Neurology* 1999;52:1908-1910. Commentary on and subsequent correspondence.

In June 1999, Drs. Frucht, Rogers, Greene, Gordon, and Fahn reported their experience with the new dopamine agonists pramipexole and ropinirole in *Neurology*. Eight of their patients with Parkinson's disease (PD) experienced sudden episodes of sleep, causing serious motor vehicle accidents. Frucht et al serendipitously noticed that at the time of their accidents, all eight were taking pramipexole (Mirapex); one patient also had an accident while taking ropinirole (Requip). These events occurred over a period of 18 months following the release of pramipexole and ropinirole into the U.S. market. Frucht et al coined the term "sleep attack" to describe this syndrome, attempting to capture the sudden and unexpected nature of these events.

There were no obvious factors (patient age, duration of Parkinson's treatment, dose or duration of exposure to pramipexole or ropinirole) that identified patients at risk for sleep attacks. In four of eight patients, the first attack occurred during driving. Only three of eight patients experienced somnolence from pramipexole prior to their accident. Frucht et al proposed that these events resembled a narcoleptic attack, and suggested the possibility that the drugs triggered these events by down-regulating dopaminergic input to the reticular-activating system.

Following its introduction into the U.S. market, pramipexole quickly became the most widely prescribed dopamine agonist for PD, and ropinirole also achieved a significant share of the agonist market. The publication of this paper generated heated responses from Pharmacia and SmithKline Beecham (the manufacturers of the drugs), as well as considerable debate from movement disorders specialists. Most of these opinions appeared recently in the correspondence of the January 2000 issue of *Neurology*.

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COMMENTARY

As the author of the original paper and summary letter of response, it would be unreasonable not to acknowledge that this paper generated significant controversy. What follows may be construed as a biased view of the issue. However, clinical reports over the last six months have lent considerable support to our original report. The central questions in this debate are listed below. I will summarize the arguments for and against each issue.

Critical Questions: The New Agonists

- Question 1: Are the new dopamine agonists (pramipexole and ropinirole) responsible for sleep attacks? Are sleep attacks different from sedation?
- Question 2: If so, how do these drugs trigger these events?
- Question 3: Are there risk factors that can reliably predict the occurrence of sleep attacks in patients taking these drugs?
- Question 4: Can pramipexole and ropinirole be used safely in patients who drive?

Answers

Answer 1: Several correspondents argued that the new dopamine agonists were not solely responsible for these events. They ascribed these attacks to the interaction of agonists with other medications, or to an underlying sleep disturbance commonly seen in PD. Several correspondents also questioned whether sleep attacks differed from sedation. They point to the known sedating effect of most dopaminergic agents, arguing that sleep attacks (if they exist) be viewed as a more severe form of sedation. This is a mistaken interpretation: "sleep attacks" have all been abrupt and sustained for seconds or more without prior anticipation.

In the six months following publication of our report, additional data have helped address these questions. More than 16 other Parkinson's patients were subsequently reported who experienced sleep attacks during treatment with pramipexole. Margaret Hoehn reported nine of her patients also were involved in motor vehicle accidents. In a letter sent to the European Union, SmithKline reported sleep attacks in 16 Parkinson's patients treated with Requip. Other observations are reported in press. It does not seem tenable to propose that these events do not occur, as they have now been reported at many centers by different neurologists. While it is true that dopaminergic agents are often sedating, similar events of sudden sleep were not reported with pergolide, despite more than a decade of worldwide use. One could ask why sleep attacks were not reported in the clinical trials of pramipexole or ropinirole. Whether events were observed but coded as sedation or whether events were even observed at all remains an open question.

Answer 2: The mechanism by which pramipexole or ropinirole triggers abrupt, unanticipated sleep is unknown. We advanced one possibility in our correspondence to *Neurology*. Pramipexole and ropinirole have enhanced affinity for the D3 subtype of dopamine receptors. This receptor has recently been shown to be important in a well-known animal model of narcolepsy. Further work is needed to resolve this issue.

Answer 3: Heated debate has addressed whether risk factors can reliably predict the development of sleep attacks. Several authors, including some of the correspondents, have proposed a maximum dose (typically 1.5 mg of pramipexole) or duration of exposure to the agonist that would safeguard against a sleep attack. Alternatively, direct and frequent questioning regarding sedation or episodes of sudden sleep is proposed as a safeguard against these events.

The data do not support these recommendations. In order to recommend a dose or duration of drug exposure that is safe, doctors should expect that if this dose is not exceeded, or if the drug is used for at least the safe period, no events should occur. Sleep attacks, however, have

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now been reported with doses of pramipexole below 1.0 mg per day. Events have also occurred more than one year after patients start the drug. Most disturbing, not all events are preceded by other events.

Answer 4: The most important issue facing a neurologist who prescribes pramipexole or ropinirole is whether these drugs can be used safely in patients who drive or perform other activities requiring constant alertness. For patients who do not drive, a sleep attack may be inconsequential; for patients who drive, it is potentially life threatening for both the patient and the public.

The European Medicines Evaluation Agency has formally recommended that patients who take these drugs abstain from driving. The Food and Drug Administration stopped short of this warning but amended the warning label of Mirapex (a similar change will probably be made shortly with Requip).

What is the proper recommendation? (There is no answer to this question at present.) It would seem prudent to discuss this issue fully with all patients who are currently taking these drugs or who begin taking them, and to fully document this conversation. Until more data are available, *Neurology Alert* urges its readers to prohibit recommending these drugs in patients who drive. **—SF**

Diabetes, Head Trauma, Marriage, and Dementia

ABSTRACTS & COMMENTARY

Sources: Ott A, et al. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* 1999;53:1937-1941; Mehta KM, et al. Head trauma and risk of dementia and AD: The Rotterdam Study. *Neurology* 1999;53:1959-1962; Helmer C, et al. Marital status and risk of AD. *Neurology* 1999;53:1953-1958.

DIABETES MELLITUS TYPE 2 (DM) INCREASES THE risk of stroke and persons with stroke are thought to be more likely to develop dementia if they suffer from diabetes. It has been suggested that DM might also be a risk factor of Alzheimer's disease (AD). Among a community-based prospective cohort study based in the Netherlands, 6370 involved participants were screened for DM and dementia, with an average follow-up period of 2.1 years. In approximately 1100 other cases with no follow-up information, dementia status was culled from medical records.

DM was found to nearly double the age- and gender-adjusted risk of dementia in 692 diabetics. The incidence risk of dementia was highest in those requiring insulin treatment, and lowest among newly diagnosed or untreated mild cases. DM incidence in men or women was about equal, with no clear trend in age. When the likely cause of dementia and other confounders was evaluated, diabetes was found to increase by two-fold the risk of both dementia in general and AD in particular.

The Rotterdam study also addressed the possibility of a relationship between mild head trauma and the development of dementia. This arm of the study included 6645 subjects, age 55 and older, who were free of dementia at the onset. Self-report of past head trauma was obtained from this cohort and incident cases of dementia were determined over the 2.1-year follow-up period. A total of 129 subjects developed dementia over this time. In concordance with some past studies, no increased risk of dementia was found as a function of exposure to head trauma with or without loss of consciousness. In contrast to earlier studies by other groups, possession of the APOE-e4 allele was not found to modify the relationship between head trauma and the development of AD.

A French research team examined the issue of whether marital status affected risk of dementia. Helmer and colleagues divided their cohort of 3675 subjects into groups of married/cohabitant, divorced/separated, widowed, and never married. Helmer et al found the relative risk of dementia was increased among the never married relative to the married individuals, and the risk was specifically associated with AD. The risk of dementia was not significantly elevated among widows and divorced subjects. The results remained significant even after taking into account potentially confounding factors such as educational achievement and wine consumption. The analysis did not permit a firm conclusion to be drawn as to whether never married persons were actually at increased risk or married persons enjoyed some protection against the disease.

COMMENTARY

These results warrant further investigation. One previous indication of a possible association between diabetes and AD came from recent studies showing increased advanced glycosylation end products (AGE) in the brain of Alzheimer's patients. Increased AGE expression is found in other end organs that are frequently affected by complications in diabetics. While there are many possible explanations for such an association, further work will be needed to confirm this observation.

The lack of an association between head trauma and dementia in this report is not surprising, in that five out

of every six studies of head trauma and dementia carried out before 1990 failed to demonstrate just such a relationship. However, more recent work has suggested an additive or even synergistic relationship between head trauma, dementia, and APOE genotype. The negative findings in this case may, in part, reflect differences in the method of ascertainment of head trauma history or another unrecognized confounding factor.

Failure to marry has not been previously implicated as a risk factor for AD. Helmer et al made a valiant effort to measure the subjects' social involvement independent of marriage, and found that level of social activity did not correlate with dementia incidence. One could postulate similar protective mechanisms for marriage as for higher education. An alternative explanation is that unmarried persons have some underlying personality trait that segregates with the propensity to develop dementia. Whatever the explanation, its somewhat comforting to know that the much-maligned institution of marriage may have benefits above and beyond joint tax returns. **—NRR**

Promising New Antistroke Treatment

ABSTRACT & COMMENTARY

Source: Slusher S, et al. Selective inhibition of NAALADase, which converts NAAG to glutamate, reduces ischemic brain injury. *Nat Med* 1999;5:1396-1402.

Excessive glutamate release in acute ischemic stroke leads to a cascade of neuronal excitotoxicity and cell death. Numerous agents, such as the glutamate receptor blocker MK-801, have been shown to attenuate this process in animals, but no drug has yet been found effective in clinical stroke trials.

The neuropeptide NAAG (N-acetyl-aspartyl-glutamate) is a glutamate receptor antagonist and is also a direct source of glutmate when it is hydrolyzed by the enzyme NAALADase (N-acetylated-a-linked-acidic dipeptidase). 2-PMPA, an inhibitor of NAALADase, may afford neuroprotection by increasing NAAG and decreasing its by-product, glutamate.

Slusher and colleagues demonstrate the following:

1. 2-PMPA inhibits cyanide-induced ischemia in tissue culture. The magnitude of this inhibition was 85%, compared with 60% for MK-801.
2. The volume of stroke produced by middle cerebral artery occlusion (MCAO) in rats was reduced by 54% with immediate 2-PMPA administration. 2-PMPA administration delayed by 60 or 90 minutes, but not 120 minutes, produced similar benefits.
3. With 2-PMPA, glutamate levels in the ischemic brain were reduced by 80% in the basal ganglia and 100% in the cerebral cortex. NAAG levels were significantly increased. There effects were not observed in non-ischemic controls.
4. No adverse behavioral or histological effects were observed (in contrast to control experiments with MK-801).

COMMENTARY

NAALDase inhibition may represent a promising "upstream" method of modifying glutamate neurotoxicity by preventing its production and increasing levels of an inhibitory precursor. This effect appears to occur specifically in the ischemic milieu. Unfortunately, in rats, the drug appears to be effective only up to 90 minutes. If a similar time profile applies in humans, it is unlikely to be of clinical use. Nevertheless, given its favorable safety profile, we look forward to human trials. **—AZS**

Another Promising New Antistroke Treatment

ABSTRACT & COMMENTARY

Source: Furlan A, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: A randomized controlled trial. *JAMA* 1999;282:2003-2011.

Thrombolysis with intravenous tissue plasminogen activator (tPA) has been shown to be beneficial when given within three hours of acute ischemic stroke. These data from the PROACT study suggest that intra-arterial (IA) recombinant prourokinase (r-proUK) may extend this therapeutic window to six hours.

A total of 180 patients were randomized in a ratio of 2:1 to receive up to 9 mg of IA r-proUK plus heparin (n = 121) or heparin only (n = 59). In the primary analysis, 40% of r-proUK patients and 25% of control patients had a modified Rankin score of 2 or less (P = 0.04). This was a 58% relative benefit. Recanalization rates were 66% for the r-proUK group and 18% for the control group (P < 0.001). Other secondary outcome measures at 90 days, such as Barthel Index of 90 or more or NIH Stroke Scale of 1 or less showed insignificant trends toward benefit. The overall hemorrhage rate was 35% with r-proUK compared to 13% in controls, while

symptomatic hemorrhage occurred in 10% and 2%, respectively. There were no differences in mortality.

COMMENTARY

Although total hemorrhage rates were high for r-proUK (often small and seen on a mandatory post-procedure CT scan), the symptomatic rate was only 10%. This is not enormously higher than in the NINDS-tPA trial (6.3%). Furthermore, the r-proUK patients were treated later and had larger strokes, both factors known to increase hemorrhage risk.

IA thrombolysis should be strongly considered for patients presenting with MCA occlusion within 3-6 hours of symptom onset. IA therapy for basilar artery occlusion might be considered up to 12 hours post-stroke. In the 0- to 3-hour time window, IV tPA remains the standard of care. However, in centers where it is available, combination IV followed by IA therapy should be considered.

r-proUK is not currently FDA approved. Current options for IA therapy include nonrecombinant urokinase (which is currently out of production) or tPA (which may be given in IA doses of approximately 20-30 mg). **—AZS**

Clinical Diagnosis of Creutzfeldt-Jakob Disease

ABSTRACTS & COMMENTARY

Sources: Poser S, et al. How to improve the clinical diagnosis of CJD. *Brain* 1999;122:2345-2351; Puoti G, et al. Sporadic CJD: Concurrence of different types of PvPsc in the same brain. *Neurology* 1999;53:2173-2176; Dickson WD, Brown N. Multiple prion types in the same brain. Is a molecular diagnosis of CJD possible? *Neurology* 1999;53: 1903-1904.

THE TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES (TSEs) include several different disorders, each caused by different prion proteins and show relatively distinct disease patterns. Most are sporadic but some are inheritable, others can be iatrogenic, and recently some appear to have been transmitted to humans from cows suffering from bovine spongiform encephalopathy. (See Scott MR, et al. *Proc Natl Acad Sci U S A* 1999;96: 15137-15142.) Hereditary forms are rare and consist of familial Creutzfeldt-Jakob disease (CJD), the Gerstman-Straussler-Sheinker syndrome, and fatal familial insomnia (FFI). Iatrogenic examples from the past include transfer of the prions by corneal transplants, reuse of deep brain electrodes previously used for EEG recordings, or dura mater obtained post-mortem from CJD patients. Several years ago, a miniepidemic of CJD occurred from injecting children with pituitary growth hormone obtained from CJD cadavers. No such person-to-person transmittal has been reported during recent years.

Sporadic CJD is a relatively rare disorder with a yearly incidence of a little more than one case per million per year. The actual occasion of sporadic CJD lacks a completely satisfactory explanation. Dickson and Brown, however, point out that the gene exists on the short arm of chromosome 20 and, in early life, generates the normal prion gene, termed PrP. They state, "Missence, deletion and duplication of the normal gene at codon 129 of Cr 20 influence expression, both inherited and, apparently, sporadic." Whether this is the ultimate, correct conclusion, time will tell.

In keeping with the above comments, Puoti and colleagues have identified two distinctly different molecular types of prion disease-specific protein (PrPsc) in five out of 15 patients dying from sporadic CJD. As Dickson and Brown point out, it may soon be possible to identify CJD exactly by tissue molecular identification. Meanwhile, noninvasive clinical diagnoses of CJD based on the clinical phenotype and supporting laboratory tests have become progressively more accurate.

Poser and colleagues have established in Gottingen, Germany, a national surveillance unit for notification of patients having possible/probable CJD. During three years (1993-96) 364 cases were reported, all accompanied by family consent for procedures. When possible, all patients had research-level, scalp-recorded EEGs, CT, and/or MRI studies and expressed mini-mental scores of less than 24. CSF samples, single or successive, were performed in most patients with emphasis on the presence or absence of the 14-3-3 protein immunoassay (source: Santa Cruz Biotech, Santa Cruz, CA). Cases were classified as probable, possible, or not CJD. Six patients were excluded from further analysis because of having a genetic prion disease.

The clinical diagnosis of CJD is usually not difficult. As the table indicates, the disease begins insidiously with either clinically recognized early dementia, unilateral signs of a combination of striatum-engendered hypertonia, cortico spinal motor dysfunction, and/or myoclonus. Routine laboratory findings or CT scans have little diagnostic value, except to rule out neoplasms or inflammatory disease of the brain. EEG findings of periodic sharp waves or MRI-identified hyperintensity of the basal ganglia strongly support

the clinical diagnosis.

The predictive table turned out to be remarkably accurate and, as the reader can see, includes only a limited but important group of clinical signs that derive from the known autopsy diagnoses. The 14-3-3 marker gave a false-positive response mostly when patients had a continued inflammatory reaction of the CNS but the number of negative errors is not given.

Regrettably, the incidence of the 14-3-3 spinal fluid is not precisely indicated in Poser et al's ultimate predictions prior to autopsy. Among 193 patients who were classified as probable CJD on the basis of clinical findings and laboratory data, about half (95) were autopsied. Only five were misdiagnosed as CJD by the presence of the 14-3-3 positively. Four of these turned out to have Alzheimer's disease and one had a primary CNS lymphoma. Fifty-four patients fulfilled the clinical criteria of CJD but lacked the specific sharp waves as EEGs. Of these, half had CJD at autopsy but Poser et al omit saying whether they had typical MRI changes. Most illnesses such as Hashimoto's encephalitis (identified by antithyroid antibodies) or Alzheimer's disease, identified by NINCDS, were omitted in advance from the study.

One hundred eleven patients were not clinically diagnosed even as possible CJD. Two turned out to have CJD, but the required galloping dementia was not apparent (one had become aphasic at 3 months). Both, however, had the 14-3-3 protein in the CSF.

Table

Clinical and Laboratory Diagnostic Features of CJD*

Rapid, progressive dementia in less than two years.
(No evidence of vascular, inflammatory, or other encephalitis)
At least two of the following somatic abnormalities must exist:
1. Myoclonus:
2. Visual and/or cerebellar ataxia;
3. Pyramidal and/or extrapyramidal signs; akinetic mutism

Laboratory signs	Sensitivity	Specificity
EEG: periodic sharp waves (n = 256)	65%	86%
MRI: basal ganglia hyperintense (n = 213)	67%	93%
14-3-3 protein in CSF (n = 289)	95%	93%

*Adapted from Poser S, et al. *Brain* 1999;122:2345-2351.

COMMENTARY

Poser et al's report is useful and provides a helpful clinical protocol that usually will lead the neurologist directly to an accurate diagnosis of CJD. Certain lapses, however, reduce the imperative value of their report. They cite the evidence that MRI brings out basal ganglia enhancement in CJD and is apparently a little more informative than the EEG in strengthening the clinical diagnosis taken together. Unfortunately, however, they omit calculating the compound probability of EEG and MRI in accurately diagnosing CJD. Furthermore, although they highly praise the 14-3-3 protein as a diagnostic tool for CJD, they don't emphasize to the reader: a) the knowledge that the protein is nonspecific for CJD; b) how specifically is it related, overall, to the individual autopsy findings, both positive or negative; and c) how often does it miss the diagnosis. Cornell-New York Presbyterian Hospital has also used the 14-3-3 protein test developed by Santa Cruz Biotech. We have not always found it positive in morphologically diagnosed cases of CJD. The test nonspecifically reacts to CNS inflammatory illnesses. It appears in early stages of such illnesses but declines as they subside, usually disappearing by two to three weeks after onset. By contrast, the molecule usually appears relatively low in the CSF early during the course of CJD but gradually rises as CJD progressed.

MRL Reference Laboratory (10703 Progress Way, Cypress, CA 90630; 800-445-4032) can process the 14-3-3 test. For the interested reader, a well-written, short, up-to-date, and comprehensive description of the fundamental biology of the prion diseases can be found in the article, "Prion protein and the transmissible spongiform encephalopathy diseases" (Chesebro B. *Neuron* 1999; 24:503-506). **—FP**

Update on Plasmapheresis in Neurological Disease

ABSTRACTS & COMMENTARY

Sources: Weinshenker BG, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. *Ann Neurol* 1999;46:878-886; Clark WF, et al. Therapeutic plasma exchange: An update from the Canadian apheresis group. *Ann Intern Med* 1999;131: 453-462.

WEINSHENKER AND COLLEAGUES PERFORMED A randomized controlled trial of plasma exchange (7 exchanges, 54 mLs/kg, 1.1 plasma vol/exchange) in 22 patients with acute severe inflammatory demyelinating disease of the central nervous system (CNS). Subjects included 12 patients with multiple sclerosis (MS), five with transverse myelitis (TM), and five with acute dis-

seminated encephalomyelitis (ADEM) or other variants. Patients with a relatively new severe neurological deficit of three to 12 weeks duration who had failed to respond to at least five days of IV corticosteroids were enrolled in a blinded, sham-controlled crossover study.

Improvement occurred with eight of 19 (42%) of the actively treated group, compared with one of 17 (6%) of the sham-treated patients. Of 13 patients who failed to improve during the treatment phase, two eventually had significant improvement in six months of follow-up. Also, four of the responders experienced relapses during a six-month follow-up period. Weinshenker et al concluded that plasmapheresis appeared to lead to functional neurologic recovery in a subset of patients with severe inflammatory CNS demyelinating disease.

An analysis of more than 100,000 plasma exchanges in the Canadian health system from 1980 to 1997 was presented by Clark and colleagues, with a helpful review of the literature. Plasma exchange was used most commonly for myasthenia gravis and chronic inflammatory demyelinating polyneuropathy. Its use for acute Guillain-Barré syndrome had declined over the past five years, which was attributed to the increased use of IVIG for this condition. Plasma exchange was rarely used for MS. Barely discernible benefits, if any, were seen in three published studies of chronic progressive MS patients, most recently by the Canadian Cooperative MS Group (*Lancet* 1991;337:441-446).

COMMENTARY

Plasmapheresis has been used over the decades in treating fulminant ADEM, showing benefit in anecdotal case reports (e.g., Kanter DS, et al. *Neurology* 1995;45: 824-827). Controlled studies of plasma exchange, however, in acute MS attacks or chronic progressive forms of MS, have not shown a significant benefit when used as an adjunct to cyclophosphamide and corticosteroids. Weinshenker et al showed in this crossover study design a possible benefit of plasma exchange in up to 42% of patients with a variety of CNS inflammatory diseases that had not responded to steroids vs. 6% of sham-treated patients. This suggests that some small subset of patients, perhaps with a pathogenic humoral component of inflammatory demyelination, could improve with plasma exchange. Nevertheless, four of the treated eight improved patients suffered new demyelinating attacks during the following six months. Weinshenker et al were unable to define any predictors of patients that were more likely to respond to this expensive (up to $18,000) and invasive form of treatment. Thus, plasma exchange should only be considered in rare catastrophic episodes of acute inflammatory demyelination with high neurologic disability that has been refractory to treatment with conventional high-dose corticosteroids and IVIG. Patients with chronic progressive MS or long-standing neurologic deficits are not candidates for such therapy, despite much recent misguided public media attention about plasma exchange for MS. —**BA**

CNS Whipple Disease with Insomnia

ABSTRACT & COMMENTARY

Source: Lieb K, et al. Insomnia for 5 years. *Lancet* 1999; 354:1966.

This one-page report underscores the protean symptoms, difficult diagnosis, and treatment of CNS Whipple's disease. A 45-year-old man had been accurately identified and treated for the intestinal form of the disease from 1989 to 1996. Gradually increasing insomnia began in 1994, at which time polysomnographic records showed a sleep duration of 265 minutes. Physical examination, EEG, and CT scan were normal. Hypnotics had little effect. Memory and mood deteriorated by 1999 and examination identified an isolated supranuclear defect in upward gaze. Monitoring showed nocturnal sleep activity to be less than 60 minutes per 24 hours. Only sleep patterns 1 and 2 appeared, leaving absent sleep patterns 3, 4, and REM. Brain MRI disclosed nonspecific white matter patches, EEG patterns slowed to 7-8 seconds, and PCR testing of CSF identified Whipple's disease. Among several drug trials, only carbamazepine brought sleep behavior back to approximately four hours per day.

COMMENTARY

Whipple's disease is rare and its brain involvement even more so. Thus, the long comment over the short index report. Early systemic symptoms consist of migratory polyarthralgia, chronic diarrhea, and unexplained fever. Progress may be slow in the non-neurologic portion of the illness but accumulates rapidly once central nervous system abnormalities express clinical symptoms. Whipple, a Johns Hopkins surgeon, identified the disease as the result of microorganisms in the gut (Whipple GH. *Johns Hopkins Hosp Bull* 1907; 18:382-391). The illness is uncommon, and clinically expressed central nervous system invasion is even less

frequent (about 5%). Neither transmission nor independent development of the illness is as yet understood. The organism has resisted culturing, but can be identified by electron microscopy or PCR testing of tissue. Using PAS stain, Sieracki and colleagues (*J Neuropathol Exp Neurol* 1960;19:70-75) first identified the bacillus within a single macrophage in CSF. Subsequently, Cohen and colleagues (*Lancet* 1996;347:329) detected it in the CSF using PCR. Mistaken diagnoses since 1963 often have identified the disease as "chronic encephalitis." According to Louis and associates, important clues to brain intrusion of the organism include gradual functional evidence of supranuclear ophthalmoplegia, dementia, somnolence, insomnia, cranial-facial myoclonus, and hypothalamic dysfunction (Louis ED, et al. *Ann Neurol* 1996;40:561-568). Myorhythmia and masticatory movements that synchronize with pendular vergent oscillations were considered pathognomonic by Louis et al. About half of affected persons suffer from gradually advancing impaired cognitive functions. Brain imaging to date has shown only nonspecific changes. Treatment has limited success; tetracycline appears best but nothing has yet been effective in the late stage of the illness.

Of interest is the severe insomnia suffered by this unfortunate man and others described in Louis et al's survey, cited above. One can also note similar examples of pathological insomnia associated with other brainstem illness (Aldrich MS, et al. *Ann Neurol* 1989;25:577-581). Aldrich and associates described 10 patients with progressive supranuclear palsy (PSP) whose nocturnal sleep ranged from 163-352 minutes (mean, 234 min). Patients with brain trauma, acute ischemia, or hemorrhage affecting the pontine midline tegmental structures often undergo severe reductions of sleep of less than 2.5 hours. Some suffer from no sleep at all and many of the others have reduced or absent REM. Many such persons retain their awareness, but may become confused or severely delirious. Markand and Dyken (*Neurology* 1976;26:769-776), for example, described two such "locked-in" examples of this stroke syndrome. Both displayed no sleep at all when twice monitored for 24 hours. Both died, and post-mortem examination confirmed the pontine tegmental abnormalities. Other examples in the pre-1990s literature demonstrate similar structural damage to the medial pontine tegmentum. Most famous of present conditions causing malignant sleeplessness, of course, is the prion disease of fatal familial insomnia in which widespread spongiform changes are found diffusely in the cerebrum. **—FP**

Correction

In the December 1999 issue of *Neurology Alert* in the article, "Continuous Deadly Brain Degeneration Follows MPTP Injection," Dr. Rosario Trifiletti was listed as the author. The author was Dr. Steven Frucht. We regret any confusion this may have caused. ❖

CME Questions

3. Epidemiological evidence suggests that the risk of developing dementia:
   a. is increased by marriage.
   b. is decreased in juvenile-onset diabetes.
   c. is decreased by head trauma.
   d. is increased among insulin-treated diabetics.
   e. is decreased in unmarried diabetics with head trauma.

4. All of the following statements regarding intra-arterial urokinase are true *except*:
   a. Relative benefit over placebo is nearly 60%, using the Rankin scale.
   b. It is beneficial up to six hours after stroke symptom onset.
   c. Outcome as measured by the NIH-Stroke Scale and Barthel Index is significantly improved at 90 days.
   d. The rate of symptomatic hemorrhage is 10%.

5. Creutzfeldt-Jakob disease has an incidence of one per million of the population, yet clinical diagnosis is usually not difficult for neurologists. Which combination of tests has the highest probability of diagnostic accuracy?
   a. Two of four physical abnormalities plus EEG usually is specific.
   b. EEG is better than MRI.
   c. MRI is equal to the 14-3-3 in sensitivity.
   d. The presence of the 14-3-3 protein is the best clinical test when physical signs suggest the illness.

6. The new dopamine agonist pramipexole (Mirapex) has:
   a. become the most widely prescribed dopamine agonist for Parkinson's disease in the United States.
   b. caused the European Medicines Evaluation Agency to recommend that patients taking it abstain from driving.
   c. possibly been linked to "sleep attacks" in patients taking the drug causing serious motor vehicle accidents.
   d. caused the FDA to amend the warning label of the drug.
   e. All of the above

In Future Issues:

EMG in Myositis