Comment on Validation of Diagnostic Criteria for Variant Creutzfeldt-Jakob Disease

Ana Lukic, MRCP,[1,2] Simon Mead, MRCP, PhD,[1,2,3] Peter Rudge, FRCP,[1,2] and John Collinge, FRCP, PhD, FRS[1,2,3]

There is no doubt that the development of diagnostic criteria has contributed greatly to epidemiological research in prion diseases, and Heath and colleagues[1] emphasize this in surveillance studies of variant Creutzfeldt-Jakob disease (vCJD). We caution, however, against a more broad application in clinical practice, particularly in governing decisions about clinical diagnosis, communication with patients/caregivers, and access to experimental therapies. The physician looking after a young patient with an unexplained rapidly progressive neuropsychiatric syndrome, dementia, or ataxia needs to make prompt clinical decisions. There are treatable alternative diagnoses, and an early firm diagnosis is essential. The pulvinar sign on magnetic resonance imaging is often not identified when patients are first imaged, and a requirement for a clinical duration of 6 months or greater makes a probable diagnosis impossible in the early stages of disease. Physicians who have cared for families affected by vCJD are aware of the complicated psychological issues generated by the perceived mismanagement of the bovine spongiform encephalopathy epidemic, which are often exacerbated by a delay or equivocation about diagnosis. Several families also choose experimental intracerebroventricular pentosan polysulfate therapy, which requires neurosurgery.

In the context of these issues, the role of tonsillar biopsy is underemphasized by Heath et al and the criteria. In our experience of 60 biopsies, by far the largest series worldwide, tonsillar biopsy has 100% sensitivity and specificity, at any stage of the disease. Prion protein deposition in the tonsil can be patchy, and at least 20 germinal centers need to be examined.[2] The number examined in 1 French case[3] reported by Heath et al may not have been adequate to avoid a false-negative result. It is notable that of the 6 most recent patients suspected clinically of having vCJD in the United Kingdom, 3 did not meet epidemiological criteria for probable vCJD while alive. Two of these patients would have been misdiagnosed as sporadic CJD according to the updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob Disease[4] criteria; typical vCJD was diagnosed at autopsy in both. In a third patient, with a heterozygous codon 129 genotype reported by Kaski et al,[5] the pulvinar sign was not thought to be present by all neuroradiologists, and no tissue was examined. It is reasonable to expect that tonsillar biopsy may have made the correct diagnosis in each of these cases.

Given experience with transfusion-associated secondary vCJD, vCJD prions are likely to be present in significant titer in human blood, a diagnostic blood test based on detection of the infectious agent is clearly possible in principle, and if technologically achieved, will necessitate a complete revision of how we approach diagnosis in this disease.

Potential Conflicts of Interest

Nothing to report.

[1]MRC Prion Unit, UCL Institute of Neurology, [2]National Prion Clinic, National Hospital for Neurology and Neurosurgery, and [3]Department of Neurodegenerative Disease, UCL Institute of Neurology, London, United Kingdom

References

1. Heath CA, Cooper SA, Murray K, et al. Validation of diagnostic criteria for variant Creutzfeldt-Jakob disease. Ann Neurol 2010;67:761–770.
2. Ironside JW, Hilton DA, Ghani A, et al. Retrospective study of prion-protein accumulation in tonsil and appendix tissues. Lancet 2000;355:1693–1694.
3. Brandel JP, Heath CA, Head MW, et al. Variant CJD in France and the United Kingdom: evidence for the same agent strain. Ann Neurol 2009;65:249–256.
4. Zerr I, Kallenberg K, Summers DM, et al. Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. Brain 2009;132:2659–2668.
5. Kaski D, Mead S, Hyare H, et al. Variant CJD in a PRNP codon 129 heterozygous individual. Lancet 2009;374:2128.

DOI: 10.1002/ana.22273

Reply

Craig A. Heath, MD,[1] Sarah A. Cooper, MD,[2] Katy Murray, MD,[1] Andrea Lowman, MB ChB (Hons), MRCP,[3] Colm Henry, MB MRCPI, MRCGP,[4] Margaret A. MacLeod, MD, MRCP,[5] Gillian E. Stewart, MB ChB,[1] Martin Zeidler, FRCP,[6] Jan M. MacKenzie,[7] James W. Ironside, FRCPath,[7] David M. Summers, MD,[1] Richard S. G. Knight, FRCP,[7] and Robert G. Will, FRCP[7]

Lukic and colleagues illustrate the difficulties faced by the clinical neurologist looking after a "... young patient with an unexplained rapidly progressive neuropsychiatric syndrome, dementia or ataxia" and highlight the importance of timely, appropriate investigations to exclude a potentially treatable cause. The process of diagnosis and the factors responsible for diagnostic delay in variant Creutzfeldt-Jakob disease (vCJD) are complex and multifactorial. A recent review of the diagnostic process in vCJD has been undertaken and shows that diagnostic delay is not the result of problems with the diagnostic criteria or specialist investigations but is mainly because of the subtle early clinical features (Heath CA, Cooper SA, Murray K, Lowman A, Henry C, MacLeod MA Stewart GE, Zeidler M, McKenzie JM, Knight RSG, Will RG. Diagnosing variant Creutzfeldt-Jakob disease: a retrospective analysis of the first 150 cases in the UK. Submitted to the *Journal of Neurology, Neurosurgery and Psychiatry*). The early manifestations of vCJD are usually insidious and on average more than 7 months pass from clinical onset before review by a neurologist (mean time from onset to neurological review = 7.4 months; 95% CI, 6.5–8 months; n = 150). Clearly, the diagnostic criteria cannot be applied until the clinical features suggest a neurological disorder and specialist investigations are

undertaken. As highlighted in our recent report,[1] brain MRI rarely fails to support the clinical diagnosis of vCJD if the most sensitive sequences are utilized (95% sensitivity; n = 150) and the diagnostic criteria may be of value in differentiating cases from those with an alternative diagnosis.

Lukic and colleagues also highlight the diagnostic value of tonsil biopsy by illustrating a number of recent cases from UK surveillance. There can be little doubt from the data provided by Lukic and colleagues and other studies that tonsil biopsy is an important diagnostic aid in vCJD.[2] The question is not whether a positive tonsil biopsy adds support for the clinical diagnosis but whether such an invasive test, with the inherent risk associated with both the procedure and anesthetic, is routinely required for confident clinical diagnosis. One patient in the UK developed a post–tonsil biopsy aspiration pneumonia and died within a few days and another required a blood transfusion after a postoperative hemorrhage. A confident clinical diagnosis of vCJD can be achieved using noninvasive investigations in the majority of cases. In addition the UK data, to date, does not suggest that diagnosis is achieved earlier using tonsil biopsy compared to brain MRI.[1]

The diagnostic criteria for vCJD have significantly utility to both researcher and clinical neurologist and if applied with rigor allow a confident clinical diagnosis in the majority of cases using noninvasive aids. In cases where diagnostic doubt remains, serious consideration should be given to tonsil biopsy.

Potential Conflicts of Interest

Nothing to report.

[1]Department of Clinical Neurosciences, Western General Hospital, Edinburgh, UK; [2]Institute of Neurological Sciences, Southern General Hospital, Glasgow, UK; [3]Department of Neurology, University Hospital, Cardiff, UK; [4]Department of Elderly Medicine, Mercy University Hospital, Cork, Ireland; [5]Department of Neurology, Aberdeen Royal Infirmary, Aberdeen, UK; [6]Department of Neurology, Victoria Hospital, Kirkcaldy, UK; and [7]National Creutzfeldt-Jakob Disease (CJD) Surveillance Unit, Edinburgh, UK

References

1. Heath CA, Cooper SA, Murray K, et al. Validation of diagnostic criteria for variant Creutzfeldt-Jakob disease. Ann Neurol 2010;67:761–767.
2. Hill AF, Butterworth RJ, Joiner S, et al. Investigation of variant Creuzfeldt-Jakob disease and other human prion disease with tonsil biopsy samples. Lancet 1999;353:183–189.

DOI: 10.1002/ana.22287

Is Pathological Gambling in Parkinson's Disease Reduced by Amantadine?

Jee-Young Lee, MD,[1] Han- Joon Kim, MD,[2] and Beom S. Jeon, MD, PhD[2]

Impulsive compulsive behaviors (ICB), such as pathological gambling (PG), compulsive shopping, binge eating, hypersexuality, and punding, are common (6–14%) complications of dopamine replacement therapy (DRT) in patients with Parkinson's disease (PD).[1] The catastrophic results of these behavioral disturbances can cause profound damage to patients and their families,[2] and effective treatment strategies remain very challenging.

Thomas and colleagues[3] recently showed that PG can be reduced by amantadine administration in a randomized double-blind crossover study involving the administration of amantadine or placebo in patients with PD who were on DRT. We would like to note that in this well-performed study 5 or 6 of the 17 subjects had disease durations of $\geq$5 years, and 5 subjects with disease durations of $\geq$5 years dropped out of amantadine treatment (according to their table and Supporting Information).[3] Therefore, that study did not fully examine the benefit of amantadine on PG in patients with long disease durations, who have a higher risk of ICB. Moreover, their study did not elucidate whether amantadine has a long-lasting benefit on PG. It may be possible to answer to these questions by examining whether PG is less prevalent in amantadine users. We previously examined the relationship between the risk of ICB and the dopaminergic medication dose in a survey using a modified version of the Minnesota Impulsive Disorders Interview.[4] Compulsive gambling and overall ICB were found in 15 (1.3%) and 118 (10.1%) of the 1167 patients, respectively.[4] As indicated in the Table, our patients had a longer PD duration and higher daily dosages of dopaminergic medications than did those of Thomas and colleagues.[3] Surprisingly, the frequency of compulsive gambling was higher in amantadine users than in nonusers (2.4% vs 0.6%, $p = 0.006$ and $p = 0.007$ by t test and Fisher's exact test, respectively). The risk of compulsive gambling behaviors as well as overall ICB appeared to increase with amantadine use (see Table) after adjusting for clinical variables including PD duration and medication dosages (for details see the legend of the Table). We therefore suggest that the results of Thomas and colleagues[3] should be interpreted with caution, and that they need to be checked in larger cohort studies involving patients with more-prolonged disease before amantadine can be considered a new agent for treating PG in PD.

Acknowledgment

This research was supported by a grant from the Seoul National University Hospital and the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (A030001) to B.S.J.

Potential Conflicts of Interest

Nothing to report.

[1]Department of Neurology, Seoul National University Boramae Hospital, [2]Department of Neurology, Seoul National University Hospital, Seoul, Korea

TABLE: Demographics of Amantadine Use and Impulse Control Behaviors

Characteristics	Total Population (n = 1167)[4]				
	Amantadine Use				
	(−) (n = 724)	(+) (n = 459)	p[a]	Compulsive Gamblers (n = 15)	Thomas and colleagues[3] (n = 17)
Sex, F/M	439/285	241/218	0.006	4/11	4/13
Age, yr	67.2 ± 9.0	61.2 ± 9.9	<0.001	58.1 ± 11.3 (42–78)	61.0 ± 1.6 (53–74)
PD duration, mo	53.7 ± 43.1	63.3 ± 49.6	<0.001	92.7 ± 80.5 (24–300)	52.4 ± 7.8 (8–106)
HY stage	2.4 ± 0.7	2.6 ± 0.8	0.002	2.5 ± 0.9 (1–4)	1.9 ± 0.2 (1–3)
Duration of L-dopa treatment, mo	53.7 ± 43.1	63.3 ± 49.6	0.001	81.6 ± 71.5 (0–244)	18.7 ± 5.7 (22–81)
Duration of DA treatment, mo	37.9 ± 38.3	43.7 ± 42.8	0.032	50.1 ± 55.2 (7–187)	47.4 ± 7.3 (8–92)
Agonist use	514 (72.2%)	336 (73.8%)	0.535	13 (86.7%)	13 (76.5%)
L-dopa Dose, mg/day	534.5 ± 358.3	588.3 ± 382.1	0.015	503.1 ± 367.2 (0–1000)	223.5 ± 49.2 (0–500)
DA Eq dose, mg/day	1.0 ± 1.3	1.1 ± 1.3	0.356	1.7 ± 1.2 (0–4.5)	1.2 ± 0.4 (0–3)
ICBs	53 (7.4%)	65 (14.3%)	<0.001		
Gambling	4 (0.6%)	11 (2.4%)	0.006		
Shopping	12 (1.7%)	17 (3.7%)	0.028	5	
Sexual behaviors	14 (2.0%)	19 (4.2%)	0.026	4	
Eating	20 (2.8%)	20 (4.4%)	0.146	3	
Punding	24 (3.3%)	25 (5.5%)	0.073	4	
Adjusted OR for compulsive gambling	Ref	4.0 (0.9–17.5)	0.063		
Adjusted OR for overall ICB[b]	Ref	1.7 (1.1–2.8)	0.031		

Data are shown as mean ± standard deviation or number (percent). ORs were shown with 95% confidence interval.
ICB was screened by modified Minnesota Impulsive Disorders Interview.[4]
[a]The comparison between amantadine user and nonuser groups by chi-square test for categorical variables and by *t* test for continuous variables.
[b]The adjustment was done for age, gender, PD duration, HY stage, duration of L-dopa and DA treatment, use of agonist, doses of L-dopa and agonist.
DA = dopamine agonist; Eq = equivalent (1mg pramipexole equals 4mg ropinirole); F = female; HY = Hoehn and Yahr; ICB = impulsive compulsive behaviors; M = male; PD = Parkinson's disease; OR = odds ratio; Ref = reference.

References

1. Lim SY, Evans AH, Miyasaki JM. Impulse control and related disorders in Parkinson's disease. Ann N Y Acad Sci 2008;1142:85–107.
2. Voon V, Fox SH. Medication-related impulse control and repetitive behaviors in Parkinson disease. Arch Neurol 2007;64: 1089–1096.
3. Thomas A, Bonanni L, Gambi F, et al. Pathological gambling in Parkinson disease is reduced by amantadine. Ann Neurol 2010;68: 400–404.
4. Lee JY, Kim JM, Kim JW, et al. Association between the dose of dopaminergic medication and the behavioral disturbances in Parkinson disease. Parkinsonism Relat Disord 2010;16:202–207.

DOI: 10.1002/ana.22289

Reply

Marco Onofrj, MD,[1,2] Laura Bonanni, MD, PhD,[1,2] Angelo Di Iorio, MD, PhD,[3] and Astrid Thomas, MD, PhD[1,2]

Drs Lee, Kim, and Jeon present an observational, retrospective analysis of their patients receiving amantadine and call for a cautious interpretation of our data,[1] which show that amantadine add-on statistically reduces compulsive gambling.

In addition to the minor statistical differences in their study (e.g., a reference cohort was used instead of a population with impulsive compulsive disorder [ICD]), we would like to point out that observational or cross-sectional studies like the

one accompanying our study[2] cannot lead to cause effect conclusions on drug efficacy as long as consistency of use, drug treatment durations, and the confounding by indication bias cannot be analyzed.[3] Any new treatment claim calls for validation and further studies. For example, the initial evidence of benefit from L-dopa in Parkinson disease (PD) was challenged by reports that showed inefficacy or side effects.[4] The key to efficacy was patient selection and dose finding.

Amantadine is a well-known and widely-used drug, even though its mechanism of action is poorly understood. Cochrane reviews and a recent treatment guideline[5,6] report insufficient evidence and low recommendation for use of amantadine in early PD,[5,6] as properly blinded studies have not been performed. The only class I level A studies were relative to amantadine use in late PD with dyskinesias.[5–7] Thus, conservative use of amantadine in early PD is warranted. Moreover, exposure to amantadine is burdened by tachyphylaxis in approximately 8 months.[7] In our study,[1] the obvious prerequisite was absence of prior exposure to amantadine. To claim that a study failed because of inappropriate patient selection is misleading.

A cross-sectional or an observational study does not yield sufficient evidence of efficacy or lack of efficacy.[3] A call for cautious interpretation of data should follow a properly designed blinded study, and we invite others to replicate or refute our data. Evidence should come from proper study designs, and we hope that an understanding of the mechanism of this widely used but inadequately understood drug will follow.

[1]Aging Research Center, Ce.S.I., "Gabriele d'Annunzio" University Foundation, and [2]Department of Neuroscience and Imaging and [3]Laboratory of Clinical Epidemiology, Geriatric Unit, Department of Medicine and Aging, University "Gabriele d'Annunzio," Chieti-Pescara, Italy

References

1. Thomas A, Bonanni L, Gambi F, Di Iorio A, Onofrj M. Pathological gambling in Parkinson disease is reduced by amantadine. Ann Neurol 2010;68:400–404.
2. Weintraub D, Sohr, M, Siderowf A, et al. Amantadine use associated with impulse control disorders in Parkinson disease. Ann Neurol 2010;68:963–968.
3. Wang O, Kilpatrick RD, Critchlow CW, et al. Relationship between epoetin alfa dose and mortality: findings from a marginal structural model. Clin J Am Soc Nephrol 2010;5:182–188.
4. Fahn S. The history of dopamine and levodopa in the treatment of Parkinson's disease. Mov Disord 2008;23:S497–S508.
5. Horstink M, Tolosa E, Bonuccelli U, et al.; European Federation of Neurological Societies; Movement Disorder Society-European Section. Review of the therapeutic management of Parkinson's disease. Report of a joint task force of the European Federation of Neurological Societies and the Movement Disorder Society-European Section. Part I: early (uncomplicated) Parkinson's disease. Eur J Neurol 2006;13:1170–1185.
6. Horstink M, Tolosa E, Bonuccelli U, et al.; European Federation of Neurological Societies; Movement Disorder Society-European Section. Review of the therapeutic management of Parkinson's disease. Report of a joint task force of the European Federation of Neurological Societies and the Movement Disorder Society-European Section. Part II: late (complicated) Parkinson's disease. Eur J Neurol 2006;13:1186–1202.
7. Thomas A, Iacono D, Luciano AL, et al. Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. J Neurol Neurosurg Psychiatry. 2004;75:141–143.

DOI: 10.1002/ana.22314

Assessment of JC Virus DNA in Blood and Urine from Natalizumab-Treated Patients

Clemens Warnke, MD,[1] Ortwin Adams, MD,[2] Hans-Peter Hartung, MD,[1] and Bernd C. Kieseier, MD[1]

Rudick and colleagues report results of assessments of JC virus (JCV) DNA in the blood of MS patients participating in natalizumab clinical trials.[1] They demonstrate positive JCV DNA findings in only 3 of 1.305 (0.2%) natalizumab-treated multiple sclerosis (MS) patients. None of these patients developed clinical progressive multifocal leukoencephalopathy (PML). In addition, they report 5 patients who developed symptoms of PML with negative JCV DNA findings prior to diagnosis. They conclude that measuring JCV DNA in blood is unlikely to be useful in predicting PML risk in natalizumab-treated MS patients.

Using the same primers applied in 1 of the 2 polymerase chain reaction (PCR) protocols of the study by Rudick and colleagues,[2] we were able to detect JCV DNA in 2 of 67 (2.98%) MS patients treated with natalizumab at our site.[3] Interestingly, 8 months after positive plasma findings, 1 of the 2 previously tested positive MS patients developed PML (Fig) with positive JCV detection in the cerebrospinal fluid.

First, we report a >10-fold higher prevalence of positive JCV plasma findings in our cohort compared to Rudick and colleagues. Second, in contrast to these authors, we demonstrate a case of positive JCV DNA findings months prior to first symptoms of clinical PML. Third, a closer look at the results of Rudick and colleagues reveals that 2 of 5 PML patients had

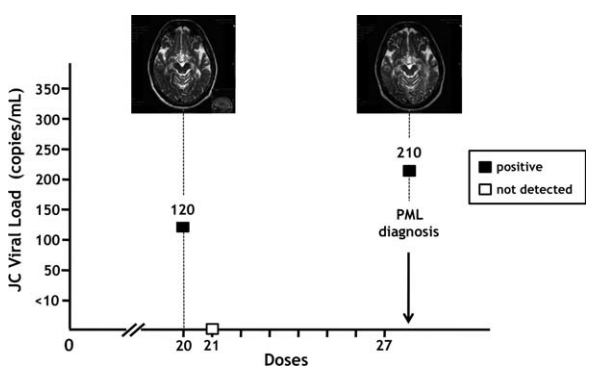

FIGURE: JC viral DNA load (copies/ml) in plasma samples collected prior to and at time of diagnosis of progressive multifocal leukoencephalopathy (PML) in a natalizumab-treated multiple sclerosis patient. Although magnetic resonance imaging (MRI) was not suggestive for PML at 20 doses of natalizumab (despite positive plasma findings), typical MRI changes were seen 8 month thereafter. Diagnosis of PML was confirmed by positive JC virus DNA detection in cerebrospinal fluid.

repeatedly undetermined PCR results prior to diagnosis; JCV DNA was detectable in 1 of 2 duplicate tests. Retests of different aliquots of the same patients were negative. Finally, these results were labeled as "not confirmed", and discussed as negative.

We do agree with the authors that currently available methods are not yet able to predict patients at risk. However, considering undetermined PCR results as positive rather than negative—together with the positive plasma PCR findings in our case—3 of 6 (50%) MS patients treated with natalizumab would be defined as plasma positive prior to developing PML. This would significantly differ from the prevalence of 0.2% or 2.98% of positive plasma findings reported by Rudick et al or by our group in patients on natalizumab without PML, suggesting a higher risk of developing PML. Clearly, further prospective studies applying standardized PCR testing are warranted to answer this question.

Acknowledgment

Part of this study was supported by the Forschungskommission of the Heinrich-Heine-University, Düsseldorf, Germany. This work was done partly as an effort within the German Competence Network of Multiple Sclerosis (KKNMS), funded by the German Ministry of Health and Education (Natalizumab Pharmacovigilance Study Group).

The technical assistance of T. Males is gratefully acknowledged.

Potential Conflicts of Interest

H.-P.H. and B.C.K. have received honoraria for lecturing, travel expenses for attending meetings, and financial support for research from Bayer Health Care, Biogen Idec, Merck Serono, Novartis, Sanofi Aventis, and TEVA. C.W. has received travel expenses from Biogen Idec for attending meetings.

[1]Department of Neurology, Heinrich-Heine-University, Düsseldorf, Germany, and [2]Institute for Virology, Heinrich-Heine-University, Düsseldorf, Germany

References

1. Rudick RA, O'Connor PW, Polman CH, et al. Assessment of JC virus DNA in blood and urine from natalizumab-treated patients. Ann Neurol 2010;68:304–310.
2. Ryschkewitsch C, Jensen P, Hou J, et al. Comparison of PCR-Southern hybridization and quantitative real-time PCR for the detection of JC and BK viral nucleotide sequences in urine and cerebrospinal fluid. J Virol Methods 2004;121:217–221.
3. Warnke C, Smolianov V, Dehmel T, et al. CD34+ progenitor cells mobilized by natalizumab are not a relevant reservoir for JC virus. Mult Scler (in press).

DOI: 10.1002/ana.22305

Reply

Richard A. Rudick, MD

The data linking development of progressive multifocal leukoencephalopathy (PML) to JCV viremia in natalizumab-treated multiple sclerosis (MS) patients is intriguing but tenuous. As Warnke pointed out, 2 of the PML cases in our article (SENTINEL Case 1 and 2)[1] had intermittent pre-PML samples designated as "not confirmed." As reported,[1] this indicated that 1 sample of a duplicate pair was positive (considered equivocal and requiring repeat testing), and that repeat testing of the same sample with the same assay was negative. It seems possible that there were low levels of JCV DNA in these pre-PML samples, but this is conjectural.

The purpose of our study was to determine whether measuring JCV DNA in blood is useful clinically; ie, could identify in advance whether a patient is going to develop PML or not. Because natalizumab-associated PML occurs in 0.1% of treated patients and 99.9% of treated patients will not develop PML, a clinically useful test would require very high predictive values. By reclassifying the "not confirmed" samples as "positive," and combining his PML case with the 5 in our report, Warnke reported that JCV DNA was measurable in pre-PML blood samples in 3 of 6 PML patients. Even with the questionable assumption that the "not confirmed" samples contained JCV DNA, this resulted in a false-negative rate of 50%.

What about false positives? A total of 205 randomly selected samples testing negative in the commercial ViraCor assay were tested using the NIH assay (Table 2 in our article[1]). Two (1%) of these samples were positive with the NIH assay, and an additional 6 (2.9%) were classified as "not confirmed." If we were to reclassify these additional cases as positive (per Warnke), then the rate of JCV viremia from the dose-suspension study would increase to 4.7% (0.8% from the commercial assay; 1% from the NIH assay; and 2.9% from the samples classified as "not confirmed" by the NIH assay). None of these patients developed PML, so these test results would be considered false positives. A test with a false-positive rate of 4.7% (to detect an event with a frequency of 0.1%) and a false-negative rate of 50% is problematic from a clinical decision-making perspective.

In our report, we classified "not confirmed" cases as negative, because the presence of JCV DNA in blood could not be confirmed on retesting. Using that conventional definition, none of the JCV DNA positive cases in our study got PML, and none of the pre-PML samples had detectable JCV DNA in blood. Therefore, as stated in our article, we do not believe that current assays are adequately sensitive and specific to achieve clinical utility in predicting PML in natalizumab-treated MS patients. Hopefully, more sensitive assays, applied to patients at higher risk for PML (eg, patients seropositive for JCV) will prove clinically useful in the future.

Cleveland Clinic Foundation,Cleveland, OH

References

1. Rudick RA, O'Connor PW, Polman CH, et al. Assessment of JC virus DNA in blood and urine from natalizumab-treated patients. Ann Neurol 2010;68:304–310.

DOI: 10.1002/ana.22309

Letter

José Luis Sandoval-Gutiérrez, MD,[1] Magali Arcos, MD,[1] Luis Alva, MD,[1] Patricia Volkow, MD,[2] Tabare Ferrari, MD,[2] Francisco Quiñones, MD,[1] Joel Vázquez-Pérez, PhD,[1] Christopher E. Ormsby, MSc,[1] Fabiola Hanssen, MD,[1] Adrian Reséndiz, MD,[3] Patricia Alcántara, MD,[4] Rogelio Pérez Padilla, MD,[1] and Edgar Bautista, MD[1]

Recently Mariotti et al[1] reported a case of acute necrotizing encephalopathy in a 2-year-old girl positive for 2009 AH1N1 pandemic influenza. The patient developed sudden fever and seizures and had an altered mental status, but the virus could not be detected in cerebrospinal fluid (CSF).

We have studied a 22-year-old woman who was previously healthy and began on November 2, 2009 with a febrile syndrome with nonproductive cough that progressed to hemorrhagic sputum. The patient was referred to our institution, the National Institute of Respiratory Diseases in Mexico City, 4 days after symptoms onset and had 74% blood O_2 saturation in room air with a chest radiograph that showed lower left lobe opacities with an alveolar pattern.

She was intubated and received mechanical ventilation, and treated with 150mg oseltamivir twice a day for 2 days, and reduced to 75mg every day due to decreased renal function. She also received 750mg cefuroxime twice a day from admission.

We tested the presence of pandemic AH1N1 with Centers for Disease Control and Prevention-approved primers and probe sets using real time polymerase chain reaction (PCR), and sequenced a NA stretch encompassing all reported drug resistance substrate and catalytic sites,[2] with the exception of R292K. We found positive tests in tracheobronchial and nasopharyngeal exudate specimens. Creatinine and creatine phosphokinase peaked on day 3 after admission, and both decreased to normal values over the next 8 days. On day 9 the patient was successfully weaned from mechanical ventilation.

Beginning on day 11 after internment, she presented generalized seizures and had to be reintubated to protect the airways. Magnetic resonance imaging of the head (Fig) showed occipital and parietal abnormalities consistent with leukoencephalopathy. Through a lumbar puncture, we extracted a CSF sample that showed 44mg/dl glucose, 34IU/l lactate dehydrogenase, and 0 white blood count. The sample was tested for pandemic AH1N1 as described above, and came out positive and without resistance mutations.

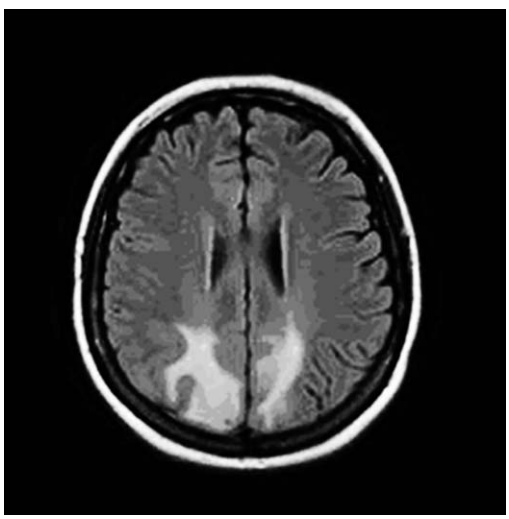

FIGURE : Magnetic resonance imaging of the patient after 11 days of hospitalization and just after seizures.

She was given a course of phenytoin and was extubated the following day. She was discharged in good health and with no neurologic sequels, with a room air O_2 saturation of 92% 4 days after leaving the intensive care unit.

The pathogenesis of influenza virus encephalopathy is not clear. The virus is rarely amplified in the CFS by PCR,[3–5] and to our knowledge this is the first report where the 2009 pandemic AH1N1 has been isolated or sequenced in this compartment. Because oseltamivir appears to penetrate the CSF inefficiently,[6] the confirmation of influenza virus in CSF opens a new diagnostic consideration for patients who have pandemic influenza-associated pneumonia in conjunction with nervous system deterioration or encephalopathy.

Potential Conflicts of Interest

Nothing to report.

[1]National Institute of Respiratory Diseases, [2]National Institute of Oncologic Diseases, [3]National Institute of Neurologic Diseases, and [4]National Autonomous University of Mexico, Mexico City, Mexico

References

1. Mariotti P, Lorio R, Frisullo G, et al. Acute necrotizing encephalopathy during novel influenza A (H1N1) virus infection. Ann Neurol 2010;68:111–114.
2. Yen H, Hoffmann E, Taylor G, et al. Importance of neuraminidase active-site residues to the neuraminidase inhibitor resistance of influenza viruses. J Virol 2006;80:8787–8795.
3. Centers for Disease Control and Prevention. Neurologic complications associated with novel influenza A (H1N1) virus infection in children—Dallas, Texas, May 2009. MMWR Morb Mortal Wkly Rep 2009;58:773–778.
4. Lyon JB, Remigio C, Milligan T, Deline C. Acute necrotizing encephalopathy in a child with H1N1 Influenza infection. Pediatr Radiol 2010;40:200–205.
5. Larcombe PJ, Moloney SE, Schmidt PA. Pandemic (H1N1) 2009: a clinical spectrum in the general paediatric population. Arch Dis Child 2011;96: 96–98.
6. Yen H, Hoffmann E, Taylor G, et al. Importance of neuraminidase active-site residues to the neuraminidase inhibitor resistance of influenza viruses. J Virol 2006;80:8787–8795.

DOI: 10.1002/ana.22293

Reply

Paolo Mariotti, MD,[1] Raffaele Iorio, MD,[2] Giovanni Frisullo, MD, PhD,[2] Domenico Plantone, MD,[2] Raffaella Colantonio, MD,[3] Tommaso Tartaglione, MD,[3] Anna Paola Batocchi, MD, PhD,[2] and Piero Valentini, MD[4]

The interesting 22-year-old patient reported by Sandoval-Gutiérrez and colleagues developed an AH1N1 infection with

lung and brain involvement, with a positive polymerase chain reaction (PCR) for AH1N1 virus on the cerebrospinal fluid (CSF). However, the case described does not resemble an acute necrotizing encephalitis (ANE), as in the case of the 2-year-old patient on which we reported.[1]

In our case, the symmetric brain lesions involving the thalami, pons, and cerebral white matter, together with clinical and biochemical findings, were consistent with ANE as previously reported by Mizuguchi and colleagues.[2] The brain magnetic resonance imaging (MRI) of the woman described by Sandoval-Gutiérrez and colleagues, showing an increased intensity of the occipital and parietal white matter, does not have the characteristic features of ANE but rather resembles a viral encephalitis.

ANE is a rare disease, characterized by the rapid development of multiple, symmetrical brain lesions. The onset of ANE is triggered by acute febrile diseases, mostly viral infection, among which influenza and exanthema subitum are the most common prodromal illness.[2]

Okumura and colleagues[3] reported that the clinical symptoms, laboratory data, and outcomes were not different between influenza and noninfluenza patients with ANE, suggesting that the pathogenetic mechanism of ANE is not dependent on infectious agents.

At present, it is unknown whether influenza virus physically enters the central nervous system (CNS) or whether neuronal and glial damage are immune-mediated. Very rarely do authors report direct evidence of influenza virus in the CNS. In a survey of 94 Japanese hospitals over 9 influenza seasons, Togashi and colleagues[4] reported that only 10% of cases had PCR detection of influenza in the cerebrospinal fluid.

The positive PCR for AH1N1 virus on the CSF in the case described by Sandoval-Gutiérrez and colleagues strongly supports the diagnosis of viral encephalitis and suggests that the H1N1 virus can physically enter the CNS. In our case,[1] the negative PCR for H1N1 in the CSF does not rule out that ANE has been triggered by the H1N1 virus, maybe by autoimmune mechanisms.

Our case[1] and the case reported by Sandoval-Gutiérrez and colleagues suggest that H1N1 influenza virus can cause CNS damage by more than 1 pathogenic mechanism.

[1]Unit of Child Neuropsychiatry, [2]Institute of Neurology, Department of Neurosciences, [3]Institute of Radiology, and [4]Institute of Paediatrics, Catholic University, Rome, Italy

References

1. Mariotti P, Iorio R, Frisullo G, et al. Acute necrotizing encephalopathy during novel influenza A (H1N1) virus infection. Ann Neurol 2010;68:111–114.
2. Mizuguchi M. Acute necrotizing encephalopathy of childhood: a novel form of acute encephalopathy prevalent in Japan and Taiwan. Brain Dev 1997;19:81–92.
3. Okumura A, Abe S, Kidokoro H, Mizuguchi M. Acute necrotizing encephalopathy: a comparison between influenza and non-influenza cases. Microbiol Immunol 2009;53:277–280.
4. Togashi T, Matsuzono Y, Narita M, Morishima T. Influenza-associated acute encephalopathy in Japanese children in 1994–2002. Virus Res 2004;103:75–78.

DOI: 10.1002/ana.22285

Reply to a Message from the Editor

Ron Cohen, MD, and Andrew R. Blight, PhD

We would like to draw your attention to a number of factual errors in the *Message from the Editor* entitled "4-Aminopyridine: New Life for an Old Drug," which was recently published in the *Annals of Neurology*.[1]

The new medicinal product that is the focus of the *Message* is Ampyra (dalfampridine extended release tablets), which was approved by the US Food and Drug Administration (FDA) in January (not March) of this year. Dalfampridine was not previously approved by the FDA, and hence there has never been a "generic forbear" in the accepted understanding of a generic drug, approved for use based on the comprehensive development program of the originator drug that it copies. The use of 4-aminopyridine (4-AP) has not been "off label," as stated in the editorial, because there was no label prior to the approval of Ampyra. The active chemical ingredient (4-AP) has been compounded for many years by some pharmacies for those patients and physicians adventurous enough to use it in the absence of regulatory approval. However, these patients and physicians did so without benefit of appropriate controls or documentation of the quality or quantity of drug provided, and without adequate evidence from randomized clinical trials to fully elucidate the risks and benefits of the compound. Recent reports have highlighted the risks of serious dosing errors associated with compounded formulations of 4-AP,[2,3] and authors of 1 report concluded that, "An error in formulation … has the potential to seriously harm a considerable number of patients" and "…preparation by the pharmaceutical industry with the infrastructure, resources, and budget to implement high standards and quality assurance may be the best method to safeguard against such medication errors."[2]

The summary of the results of the phase 3 trials provided in the second paragraph of the *Message* was not taken from the published or submitted trial reports,[4,5] but appears to have been taken from a "reanalysis" of the data performed by an FDA statistician in a briefing document submitted to the FDA Advisory Committee meeting in October 2009, a meeting that culminated in a nearly unanimous recommendation for approval of the drug. The numbers provided do not accurately reflect the average change in walking times experienced by the patients, but appear to have been derived by an unusually complex, post hoc manipulation of a subset of the trial data. More importantly, this analysis was not a planned outcome of the study, and for good reason: the study focused on those patients who responded with a consistent improvement in walking speed, because this drug, like many others, is not effective in all patients, and the day-to-day variability in functional capacity of people with multiple sclerosis (MS) means that consistency helps to identify changes as due to treatment rather than

random variability. In the 37.6% of patients who qualified as timed walk responders to dalfampridine across the 2 studies, there was an average 25.0% improvement in walking speed, compared to 6.5% in placebo-treated patients and 7.0% in dalfampridine-treated nonresponders. The clinical meaningfulness of this improvement in the responder groups was reflected by a significant reduction in self-assessed walking disability, using the 12-Item MS Walking Scale.[4] The FDA advisory panel and the FDA itself also responded favorably to the significantly increased percentage of patients in the treatment versus the placebo groups who showed 10, 20, and 30% improvements in average walking speed. This information, not the subanalysis to which you refer, was incorporated in the clinical experience section of the product label that was approved by the FDA.[6]

The *Message* states that "a 25-foot walk takes approximately 6 seconds normally." Although a 25-foot walk at comfortable walking speed requires on average about 5.5 seconds for healthy individuals, the Timed 25-Foot Walk, as performed under the directions of the Multiple Sclerosis Functional Composite,[7] measures maximum walking speed. This varies with age, so that healthy people generally complete the Timed 25-Foot Walk in approximately 3 seconds in their 20s and approximately 4 seconds in their 50s and 60s.[8]

Multipage advertisements in professional journals, particularly for newly launched drugs, are not at all unusual as a means of increasing awareness among busy physicians, so it is difficult to understand why this should be considered "rare." In fact, multipage advertisements are made necessary in part by the quite reasonable regulatory requirement that promotional activity for prescription drugs present the risks and benefits in a full and balanced way.

The clinical development of dalfampridine extended release tablets required approximately 20 years of research, investment of many hundreds of millions of dollars, the time and effort of hundreds of dedicated researchers and healthcare professionals, >2,000 volunteers, and a total of 55 clinical studies. These addressed not just efficacy but safety in all its aspects, as well as pharmacokinetics, optimal dosing, potential for drug interactions, food effects, and many other questions important for patient welfare. To say that this drug "could have been launched in the 1980s" ignores the complexities of drug development and the regulatory process. Particularly troubling to us, it ignores the fact that, prior to completion of the Ampyra development program, there were no definitive data to support the therapeutic use of dalfampridine; an independent, systematic review by the Cochrane Collaboration of published research in 2002 concluded that "no unbiased statement can be made about the safety or efficacy of aminopyridines for treating MS."[9]

To say that "development of a proprietary version was not the highest need in the field" suggests that there was an approved nonproprietary version, but there was not and is not to this day. The idea that a "more selective" channel blocker would "represent a far more promising avenue for therapy of conduction block than 4-AP" overlooks the fact that we do not yet know the nature of the particularly sensitive potassium channels responsible for the therapeutic effects of 4-AP. For all that is currently known, the clinical effects seen with dalfampridine may be the best that can be achieved with ion channel blockade for axonal conduction deficits. It would not have been reasonable to undertake an open-ended, perhaps decades-long program of research to improve upon a drug that had not successfully been brought to the clinic in the first place. Indeed, clinical development of a new drug candidate, which it was hoped would improve on the effects of dalfampridine, was recently discontinued by another company after >15 years of effort and many millions of dollars of investment, again underscoring the formidable risks and expense associated with developing innovative drugs.

The *Message* also takes issue with what it deems to be too high a cost of the drug. Such costs are made necessary by the fact that pharmaceutical companies must typically obtain a return on their development investments in a period of only a few years. They are given relatively short periods of ownership of their intellectual property, including the rights to large amounts of expensive and often hard-won data, so that society may subsequently benefit from access to less expensive generic equivalents. Costs to individual patients for new drugs are often offset by the company, through copay mitigation and patient assistance programs for uninsured and underinsured patients, so that people who cannot otherwise afford the drug may receive it at reduced or no cost. Indeed, both of these mechanisms are in effect for Ampyra.

The *Message* ends with an interesting conundrum. You suggest that "powerful incentives need to be in place to encourage the pharmaceutical industry … to take risky bets on the most pressing healthcare needs" and conversely you state that we need a "system that rationally prices drugs." Yet it is the current system for pricing of innovative drugs that provides the "powerful incentive" to the pharmaceutical industry to take risky bets in the search for real advances in healthcare. It is difficult to accept the resultant pricing as "irrational," given the free market that exists and the strictly limited exclusivity that is granted to developers of valuable therapeutics, as compared with the temporally nearly limitless return on investment provided to creators of copyrighted works such as action movies and ringtone jingles. This is a system that has worked well over the years to provide remarkable medical innovations to patients and their physicians, although it is coming under severe strain as the costs and risks of development rise faster than the profits to be made for investors, who have other choices.

Potential Conflicts of Interest

Ron Cohen and Andrew Blight are employed full time by and are shareholders in Acorda Therapeutics, Inc., the developer of Ampyra.

Acorda Therapeutics, Hawthorne, NY

References

1. Hauser SL, Johnston SC. 4-Aminopyridine: new life for an old drug. Ann Neurol 2010;68:A8–A9.

2. Burton JM, Bell CM, O'Connor PW. 4-Aminopyridine toxicity with unintentional overdose in four patients with multiple sclerosis. Neurology 2008;71:1833–1834.
3. Schwam E. Severe accidental overdose of 4-aminopyridine due to a compounding pharmacy error. J Emerg Med 2009; published online (DOI: 10.1016.2009.04.037).
4. Goodman AD, Brown TR, Krupp LB, et al. Sustained-release oral fampridine in multiple sclerosis: a randomized, double-blind, controlled trial. Lancet 2009;373:732–738.
5. Goodman AD, Brown TR, Edwards KR, et al. A phase 3 trail of extended release oral dalfampridine in multiple sclerosis. Ann Neurol 2010;68:494–502.
6. Ampyra [dalfampridine] extended release tablets prescribing information. Hawthorne, NY: Acorda Therapeutic. January 2010. Available at: http://www.ampyra.com/local/files/PI.pdf. Accessed November 26, 2010
7. Fischer JS, Jak AJ, Kniker JE, et al. Multiple Sclerosis Functional Composite (MSFC): Administration and Scoring Manual. Available at: http://www.nationalmssociety.org/for-professionals/researchers/clinical-study-measures/msfc/index.aspx. Accessed November 26, 2010
8. Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants. Age Aging 1997;26:15–19.
9. Solari A, Uitdehaag B, Guiliani G, et al. Aminopyridines for symptomatic treatment in multiple sclerosis [review]. Cochrane Database Syst Rev 2002;(4):CD001330.

DOI: 10.1002/ana.22322

Reply

The effectiveness relative to cost of any new therapy will certainly become an increasingly important consideration as future health care decisions and priorities are decided upon; this is especially true for therapies that involve, directly or indirectly, some cost to the public. We thank Dr. Cohen for lending his perspective, and that of his colleagues at Accorda Therapeutics, on 4 aminopyridine. We welcome the views of others on this specific issue, as well as on the larger topic of the cost-effectiveness of new therapies for neurologic disorders.

Stephen L. Hauser MD, and S. Claiborne Johnston MD, PhD

DOI: 10.1002/ana.22375