Dopaminergic dysfunction in unrelated, asymptomatic carriers of a single parkin mutation

To the Editor: We read with interest the article by Khan et al.¹ The authors studied asymptomatic parkin heterozygotes by 18F-dopa PET and found a significant reduction of uptake in putamen, caudate, dorsal and ventral midbrain. An interesting observation relates to the subtle extrapyramidal symptoms in four of these "asymptomatic" carriers. The authors recommended follow-up to verify whether they develop parkin disease.

One of our patients with a single parkin mutation developed parkin disease 23 years after the manifestation of tremor as the only symptom. This 56-year-old man is the only child of nonconsanguineous parents of European Jewish origin. At age 13, left hand tremor was noticed. Tremor severity remained unchanged for 23 years (without treatment), until the age of 36, when he experienced prominent rest tremor and bradykinesia of the left limbs.

Five years later, L-dopa was initiated with excellent response. Dyskinesias occurred 3 years after L-dopa onset, necessitating a left pallidotomy 18 years later. Brain MRI was normal. Genetic testing revealed a heterozygous C to T transition at nucleotide position 1197 of parkin gene (exon 10).

Parkin disease presents as slowly progressive parkinsonism.^{2,3} Even if significant dopaminergic dysfunction appears in PET studies of single parkin mutation carriers, other mechanisms and the amount of intact dopamine store at a young age might be compensatory to prevent early clinical expression.¹

However, this explanation may only relate to some patients. Others might develop parkin disease earlier, as occurred in another of our sporadic patients who carries a single parkin mutation. This 36-year-old woman is the only child of nonconsanguineous parents of European Jewish origin. At the age of 31, she experienced left foot dystonia, slowing of her left hand accompanied by rest tremor, which

later progressed to bilateral parkinsonism. Response to L-dopa given 5 years after disease onset was excellent. Brain MRI was normal. A heterozygous deletion of exon 7 of parkin was found.⁴

Haploinsufficiency (reduction in normal protein function) and dominant negative effects (nonfunctional polypeptide physically interferes with normal protein) proposed as causes of dopaminergic cell dysfunction¹ or the inhibition of parkin's ubiquitin 3 ligase activity by S-nitrosylation⁵ are probably not the only explanations. Other genetic or environmental factors might predispose carriers of a single parkin mutation not only to late-onset but also to young-onset Parkinson disease.

Rivka Inzelberg, MD, Nobutaka Hattori, MD, Yoshikuni Mizuno, MD, *Hadera, Israel*

Editor's Note: The authors had the opportunity to respond to this Correspondence but declined.

Copyright © 2005 by AAN Enterprises, Inc.

References

1. Khan NL, Scherfler C, Graham E, et al. Dopaminergic dysfunction in unrelated, asymptomatic carriers of a single parkin mutation. *Neurology* 2005;64:134–136.
2. Nisipeanu P, Inzelberg R, Abo Mouch S, et al. Parkin gene causing benign autosomal recessive juvenile parkinsonism. *Neurology* 2001;56:1573–1576.
3. Inzelberg R, Hattori N, Nisipeanu P, et al. Camptocormia, axial dystonia, and parkinsonism: Phenotypic heterogeneity of a parkin mutation. *Neurology* 2003;60:1393–1394.
4. Inzelberg R, Nisipeanu P, Carasso RL, Blumen SC, Hattori N, Mizuno Y. Early-onset parkinsonism in heterozygous parkin mutation carriers. *Ann Neurol* 2004;56(suppl 8):S28.
5. Choung KKK, Thomas B, Li X, et al. S-nitrosylation of parkin regulates ubiquitination and compromises parkin's protective function. *Science* 2004;304:1328–1331.

fMRI reveals large-scale network activation in minimally conscious patients

To the Editor: We read Schiff et al.'s article with great interest.¹ We conducted a case study regarding the application of fMRI to a patient in a minimally conscious state.² The Schiff et al. article appears to corroborate our findings of multisensory and cognitive fMRI BOLD responses in an overtly unresponsive brain-injured patient. These initial reports probing the minimally conscious state with imaging methods offer intriguing possibilities, and indeed the 2001 fMRI case study closely correlated with the patient's eventual recovery. Further research in this area is warranted.

Chad H. Moritz, PhD, *Madison, WI*

To the Editor: Schiff et al.¹ reported that two severely brain-injured patients monitored with fMRI showed brain responses to auditory personal narratives but not when the input was presented in reverse, meaningless form. A similar study³ with equally remarkable results was carried out more than 20 years earlier, ironically also by researchers at Columbia University. That it was overlooked by Schiff et al. is an indication of the obscurity into which this study has undeservedly fallen.

In the earlier report of Boyle and Greer, three brain-injured patients with disabilities at least as severe as those in the Schiff et al. study were examined. In place of monitoring by fMRI, operant conditioning was used to increase small spontaneous responses made by each patient including eyelid, finger, or mouth movements. The reinforcer in each case was the playing of a 15-second sample of music identified as the patient's favorite, presented contingent on an occurrence of the target response. A multiple-baseline design with reversal,⁴ a technique of the field of applied behavior analysis, was used to assess causal relationships. The authors reported good evidence of learning for the first patient, lesser but suggestive evidence for the second, and little evidence of learning for the third.

The first patient subsequently recovered from the vegetative state to a limited extent, the second did not recover, and the third died within 1 week after the end of testing. Thus successful operant conditioning may possibly predict recovery and may even help produce it.

Schiff et al. concluded in their later study that their findings of changes in brain activity in response to meaningful auditory input "raise important questions related to whether MCS [minimally conscious state] patients have a greater capacity to experience subjective states but also to benefit from therapeutic intervention." The results of the Boyle and Greer study raise the same questions, but go one step further by showing an actual change in behavior in response to reinforcement by emotionally meaningful stimuli.

Although the methods differ, the results of the two studies complement each other. Both methods should be exploited as valuable tools towards the goals of understanding and enhancing the capabilities of the brain-injured, minimally conscious patient.

Stephen L. Black, PhD, *Lennoxville, Canada*

Editor's Note: The authors had the opportunity to respond but declined.

Copyright © 2005 by AAN Enterprises, Inc.

References

1. Schiff ND, Rodriguez-Moreno D, Kamal A, et al. fMRI reveals large-scale network activation in minimally conscious patients. *Neurology* 2005;64:514–523.
2. Moritz CH, Rowley HA, Haughton VM, Swartz KR, Jones J, Badie B. Functional MR imaging assessment of a non-responsive brain injured patient. *Magn Reson Imaging* 2001;19:1129–1132.
3. Boyle ME, Greer, RD. Operant procedures and the comatose patient. *J Appl Behav Anal* 1983;16:3–12.
4. Kazdin A. *Behavior Modification in Applied Settings*, 6th ed. Belmont, CA: Wadsworth; 2001.

Reasons for exclusion from thrombolytic therapy following acute ischemic stroke

To the Editor: We believe that another important issue should be included in the discussion of the Cocho et al.'s article.¹ There was a narrow therapeutic window of intravenous t-PA in patients with acute ischemic stroke in the Cocho et al. study (only 44.8% were eligible for intravenous t-PA therapy). Further studies using more adequate designs (i.e., randomized controlled trials) are needed to clarify the role of this thrombolytic agent in the intra-arterial approach after 3 hours.

Prourokinase is currently the only drug adequately tested in intra-arterial treatment for acute ischemic stroke² and should be considered as the gold standard for new treatments. However, it is not easily available in most stroke unit centers around the world.

Pedro Schestatsky, Paulo Dornelles Picon, *Porto Alegre, Brazil*

To the Editor: We welcome this important discussion regarding exclusions from thrombolytic therapy in acute ischemic stroke.¹ We agree that rt-PA is not used enough for the treatment of ischemic stroke, especially in the United States, which has had drug approval longer than in Europe.

The authors reported that approximately half of their stroke patients arrived at their hospital within 3 hours from symptom onset. We have studied arrival times extensively within the Greater Cincinnati/Northern Kentucky population of 1.3 million,³ a nine-hospital system in Cleveland,⁴ as well as a US state-based stroke registry, encompassing 98 hospitals of varying size and character (personal communication, Reeves et al., 2005). We found that only 15 to 22% of patients with ischemic stroke arrive within 3 hours. More importantly, comparing arrival times in 1993 and 1999, the percentage of patients arriving within 3 hours only increased from 18% to 20%,⁵ despite numerous national and local public awareness campaigns.

Based on our data, expansion of the time window for acute treatment to 8 hours is not likely to result in significantly increased rates of acute treatment, as only 8% of all ischemic stroke patients arrive within 3 to 8 hours poststroke.⁵

We have also investigated characteristics of patients arriving promptly after stroke onset but not treated with thrombolytic therapy. In the Ohio Coverdell registry,⁶ only 171 of the 1,066 ischemic strokes (16%) presented within 2 hours of symptom onset. Of those, 20 received rt-PA, and 69 had no recorded contraindication. Patients who did not receive tPA in this group were more likely to be at small hospitals, community settings, or hospitals without stroke team involvement. The most commonly listed exclusions for these non-treated patients were time (despite arriving early) and mild stroke severity.

Therefore, while we agree that it is extremely important to minimize delays within the hospital system, we would like to emphasize that the delay in patient arrival to the emergency department remains the most important exclusion for rt-PA. This has recently been confirmed by the California Coverdell registry, published in the same issue of *Neurology*, which found that increasing early arrival of patients with stroke would hypothetically increase thrombolytic treatment by orders of magnitude more than other interventions, including the presence of stroke teams and prompt medical evaluation.⁷ Public awareness regarding stroke warning signs and plans of action require more focused study, so that more patients with stroke can benefit from rt-PA.

Dawn O. Kleindorfer, MD, Pooja Khatri, MD, Irene Katzan, MD, *Cincinnati, OH*

Reply from the Author: We thank Dr. Schestatsky et al. for their comments. We agree that the narrow therapeutic window is the main limitation for intravenous t-PA treatment and that intra-arterial prourokinase is a correct alternative for patients arriving at a hospital more than 3 hours after stroke onset.

However, in our center this therapy is not always available and few patients can benefit from this treatment. The main objective in our study was to analyze the reasons for exclusion from intravenous t-PA in order to increase the number of eligible patients. Although intra-arterial prourokinase should be considered

in randomized controlled trials in patients after 3 hours stroke onset, other treatments may also be adequate.

Mechanical embolus removal,⁸ for example, has a rate of 41 to 48% of recanalizations⁹⁻¹⁰ in the first 6 to 8 hours of stroke onset as compared to 66% with intra-arterial prourokinase,² and a rate of symptomatic intracerebral hemorrhage of 2.9% as compared to 10%.

We agree that further randomized controlled studies are needed to investigate the benefits of the new treatments that are becoming available.

We also thank Dr. Kleindorfer et al. for their comments. We agree that the delay in patients' arrival at the emergency department is the main reason for exclusion from t-PA. In our study, 44% of stroke patients arrived within 3 hours of stroke onset.

These results are discordant with the percentages reported in some studies (18 to 20%)^{3,4} and in agreement with others.^{11,12} One explanation for this high percentage may be that the results are those of a single institution, geographically situated within the Barcelona city center, with a prehospital stroke code system which was implemented 6 years ago.¹³

However, our main finding is that although a high percentage of patients reached the hospital within 3 hours of symptom onset, t-PA treatment was administered in only 7%, and 18% were excluded for avoidable reasons. The delay in hospital arrival could be shortened through national and local awareness campaigns, but if the patients are not treated promptly on hospital arrival due to intrahospital delays or other avoidable reasons, such campaigns will be ineffective.

It is important that each center analyzes its reasons for excluding patients from thrombolytic therapy. We agree with Dr. Kleindorfer et al. that the presence of stroke teams and prompt medical evaluation could increase the application of thrombolytic treatment.

Dolores Cocho, MD, *Barcelona, Spain*

Copyright © 2005 by AAN Enterprises, Inc.

References

1. Cocho D, Belvis R, Marti-Fabregas J, et al. Reasons for exclusion from thrombolytic therapy following acute ischemic stroke. *Neurology* 2005; 64:719-720.
2. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: A randomized controlled trial. Prolase in Acute Cerebral Thromboembolism. *JAMA* 1999; 282:2003-2011.
3. Kleindorfer D, Kissela B, Schneider A, et al. Eligibility for recombinant tissue plasminogen activator in acute ischemic stroke: A population-based study. *Stroke* 2004;35:e27-29.
4. Katzan IL, Hammer MD, Hixson ED, Furlan AJ, Abou-Chebl A, Nadzam DM. Utilization of intravenous tissue plasminogen activator for acute ischemic stroke. *Arch Neurol* 2004;61:346-350.
5. Kleindorfer D, Alwell K, Khoury, et al. Temporal Trends in emergency department arrival times for acute ischemic stroke: A population-based study. *Stroke* 2005;36:494.
6. Khatri P, Kleindorfer D, Moomaw C, et al. Characteristics of stroke patients without rt-PA treatment despite prompt presentation. Accepted for poster presentation; 57th annual meeting of the American Academy of Neurology; 2005.
7. California Acute Stroke Pilot Registry Investigators. Prioritizing interventions to improve rates of thrombolysis for ischemic stroke. *Neurology* 2005;64:654-659.
8. Gobin P, Starkman S, Duckwiler G, et al. MERCI 1. A phase 1 study of mechanical embolus removal in cerebral ischemia. *Stroke* 2004;35: 2848-2854.
9. Berlis A, Lustsep H, Barnwell S, et al. Mechanical thrombolysis in acute ischemic stroke with endovascular photoacoustic recanalization. *Stroke* 2004;35:1112-1116.
10. Wikholm G. Transarterial embolectomy in acute stroke. *AJNR Am J Neuroradiol* 2003;24:892-894.
11. Smith MA, Doliszny KM, Shahar E, McGovern PG, Arnett DK, Luepker RV. Delayed hospital arrival for acute stroke: the Minnesota Stroke Survey. *Arch Intern Med* 1998;129:190-196.
12. Morris DL, Rosamond W, Madden K, Schultz C, Hamilton S. Prehospital and emergency department delays after acute stroke: The Genentech Stroke Presentation Survey. *Stroke* 2000;31:2585-2590.
13. Belvis R, Cocho D, Marti-Fabregas J, et al. Benefits of a prehospital stroke code system. Feasibility and efficacy in the first year of clinical practice in Barcelona, Spain. *Cerebrovasc Dis* 2005;19:96-101.

Episodic third nerve palsy with cryptococcal meningitis

To the Editor: Azran et al. have postulated transient ischemic neuropathy associated with mycotic vasculitis as the mechanism for this rare presentation of episodic third nerve palsy. However, a closer examination of the photomicrograph shows scanty small capillaries with no evidence of vasculitis.¹

What may be seen is a conglomerate of inflammatory cells including lymphocytes, histiocytes, and macrophages, some of which contain cryptococcal organisms.¹ The absence of any vasculitic loci in the histological section will undoubtedly make the ischemic neuropathy postulation dubious. Interestingly, contrary to the authors' supposition, increased intracranial pressure has been shown to play an important role in the morbidity and mortality of cryptococcal meningoencephalitis.²

David T.L. Liu, MRCS, Paul C.L. Choi, MB, ChB, FRCP(A),
Alice Y.K. Chan, *Hong Kong*

Reply from the Authors: In our case report of a patient with episodic painful third nerve palsies and cryptococcal meningitis,¹ we postulated that transient ischemia of the third nerve itself via

vasculitis may explain the recurrent episodes of third nerve palsies. Liu et al. disagreed, mostly based on the fact that the figure shown in the article does not show vasculitis but only inflammatory cells and cryptococcal organisms.

As indicated in our case report, evidence of vasculitis around the cranial nerves was found at autopsy. As neuro-ophthalmologists dealing with chronic papilledema secondary to very elevated intracranial pressure in the setting of cryptococcal meningitis, we are very aware of the important role of increased intracranial pressure in the morbidity and mortality of cryptococcal meningitis. The clinical presentation in our patient did not support a direct role of increased intracranial pressure in the occurrence of these episodes of painful third nerve palsies.

Valerie Biousse, MD, Nancy J. Newman, MD, *Atlanta, GA*

Copyright © 2005 by AAN Enterprises, Inc.

References

1. Azran MS, Waljee A, Biousse V, Frankel M, Newman NJ. Episodic third nerve palsy with cryptococcal meningitis. *Neurology* 2005;64:759–760.
2. Fries BC, Lee SC, Kennan R, Zhao W, Casadevall A, Goldman DL. Phenotypic switching of *Cryptococcus neoformans* can produce variants that elicit increased intracranial pressure in a rat model of cryptococcal meningoencephalitis. *Infect Immun* 2005;73:1779–1787.

Corrections

Systemic autoantibodies against discrete inner ear compartments in bilateral vestibular loss

In the Clinical/Scientific Note “Systemic autoantibodies against discrete inner ear compartments in bilateral vestibular loss” (*Neurology* 2005;65:167) by Årup et al., there are errors in some of the references to the figure. Except for the first reference to the figure, showing partial matching of bands between serum and CSF, all other references should have been to the table, not to the figure. The table, which is published in the data supplement on the *Neurology* Web site (www.neurology.org), correctly reports the location in individual ear compartments of the serum antibodies from the two patients with bilateral vestibular loss. The authors apologize for this oversight.

In Memoriam: Donald Winston Paty, MD, FRCPC (1936–2004)

The In Memoriam “Donald Winston Paty, MD, FRCPC (1936–2004)” (*Neurology* 2005;65:984–985) by Joël Oger contains two misspelled names. The correct names are Jack Foster and Peter Hudgson.

Neurology®

Corrections

Neurology 2005;65;1845-1845-a
DOI 10.1212/WNL.65.11.1845-a

This information is current as of December 12, 2005

Updated Information & Services

including high resolution figures, can be found at:
<http://n.neurology.org/content/65/11/1845.2.full>

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints

Information about ordering reprints can be found online:
<http://n.neurology.org/subscribers/advertise>

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright . All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.