Stiff person syndrome with cerebellar disease and high-titer anti-GAD antibodies

To the Editor: Rakocevic et al.¹ report 5 out of 38 consecutively studied patients with stiff person syndrome (SPS) and high-titer anti-GAD antibodies who also developed cerebellar disease. We would like to highlight the issue of eye movement abnormalities in those patients, and commend them on including that information.

The authors reported that in Patient 1, hypometric saccades were prominent; Patient 2 had square-wave nystagmus; Patient 4 had nystagmus and hypometric saccades; and Patient 5 had impaired eye movements. They did not mention ocular motor abnormalities in Patient 3. They again introduced ocular motor abnormalities in the Discussion, stating that "Gait or focal limb ataxia, dysarthria, and visual disturbances were prominent in all patients. Slow and hypometric saccades and sustained lateral gaze-evoked nystagmus were common."

Unfortunately, the documentation and discussion of eye movement disturbances in SPS and in cerebellar ataxia with GAD antibodies is rare and is usually based on vague, nonquantitative, clinical descriptions.² Economides and Horton³ were the first to objectively report the presence of gaze-holding nystagmus, limited abduction, ocular misalignment, deficient smooth pursuit, and impaired saccadic initiation in a patient with SPS. They attributed these findings to a dysfunction of GABAergic pathways.

Using the magnetic search coil technique, we recently reported a detailed quantitative documentation of a rare saccade velocity profile, downbeat nystagmus, and loss of downward smooth pursuit in a patient with SPS and cerebellar ataxia.⁴ Additional studies using precise measurement of eye movements in SPS patients with and without cerebellar signs could be useful in clarifying the link between GAD antibodies and cerebellar dysfunction. The possibility of using quantitative eye measures as a biomarker of neurodegeneration has been discussed⁵ regarding the assessment of eye movements in presymptomatic and symptomatic individuals with Huntington disease.

We would like to encourage the authors and the neurologic community to quantitatively study eye movements in SPS patients with and without cerebellar signs and in cerebellar ataxia with GAD antibodies.

C.R. Gordon, A.Z. Zivotofsky, T. Siman-Tov, N. Gadoth, *Kfar Saba, Israel*

Disclosure: The authors report no conflicts of interest.

Reply from the Author: Gordon et al. emphasize that abnormal eye movements can occur in patients with SPS and cerebellar ataxia. We agree. We have observed such abnormalities not only in patients with SPS and cerebellar ataxia reported in our present series,¹ but also in some SPS patients without ataxia. The association is highlighted even further by another patient we have recently seen who presented only with nystagmus and saccadic eye

movement abnormalities and positive GAD antibodies, but without signs of SPS.

These observations indicate that GABAergic pathways are involved in abnormal eye movements. We also agree with Gordon et al. that the eye movements need to be studied quantitatively and serially in SPS patients, but do not believe that GAD antibodies provide an etiologic link with this phenomenon. As we have repeatedly discussed, GAD is a cytosolic antigen and antibodies directed against intracellular antigens are not pathogenic.⁶⁻⁸ In SPS, anti-GAD antibodies are only disease markers suggesting GABAergic dysfunction.^{6,7}

There is a need to search for other autoantigens, possibly a surface antigen, responsible for these patients' symptomatology. Towards this goal, we have recently identified the GABAA-receptor associated protein (GABARAP) as one such autoantigen because up to 70% of SPS patients, including those with ataxia and abnormal eye movements, have circulating anti-GABARAP antibodies.⁹ Because these patients' IgG inhibited the surface expression of GABAA-receptor in vitro, we have proposed that anti-GABARAP antibodies may play a role in the patients' symptomatology.⁹

The GABAergic system is therefore a target for an autoimmune attack resulting in various manifestations including SPS, cerebellar ataxia, and abnormal eye movements. Because such disorders are amenable to immunotherapy, clinical vigilance to identify them early in the disease course is strongly suggested.

Marinos C. Dalakas, *Bethesda, MD*

Disclosure: The author reports no conflicts of interest.

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References

1. Rakocevic G, Raju R, Semino-Mora C, Dalakas MC. Stiff person syndrome with cerebellar disease and high-titer anti-GAD antibodies. *Neurology* 2006;67:1068-1070.
2. Honnorat J, Saiz A, Giometto B, et al. Cerebellar ataxia with anti-glutamic acid decarboxylase antibodies. *Arch Neurol* 2001;58:225-230.
3. Economides JR, Horton JC. Eye movement abnormalities in stiff person syndrome. *Neurology* 2005;65:1462-1464.
4. Zivotofsky AZ, Siman-Tov T, Gadoth N, Gordon CR. A rare saccade velocity profile in stiff-person syndrome with cerebellar degeneration. *Brain Res* 2006;1093:135-140.
5. Biglan KM, Halmagyi M. The eyes as a window into disease prevention. *Neurology* 2006;67:376-377.
6. Dalakas MC, Fujii M, Li M, McElroy B. The clinical spectrum of anti-GAD antibody-positive patients with stiff-person syndrome. *Neurology* 2000;55:1531-1535.
7. Dalakas MC, Li M, Fujii M, Jacobowitz DM. Stiff-person syndrome: quantification, specificity and intrathecal synthesis of GAD65 antibodies. *Neurology* 2001;57:780-785.
8. Dalakas MC, Fujii M, Li M, Lutfi B, Kyhos J, McElroy B. High-dose intravenous immunoglobulin for stiff-person syndrome. *N Engl J Med* 2001;345:1870-1876.
9. Raju R, Rakocevic G, Chen Z, et al. Autoimmunity to GABARAP in stiff-person syndrome. *Brain* 2006 Sep 19 [epub ahead of print].

Multifocal motor neuropathy with and without conduction block: A single entity?

To the Editor: Delmont et al.'s recent report¹ provides a compelling case that motor neuropathies responsive to IVIg may not demonstrate conduction block (CB) on conventional nerve conduction studies (NCS). Drs. Chaudhry and Swash concurred with a previous report that distal demyelination with secondary axon loss may be responsible for this finding.^{2,3}

Both publications advocate an empiric IVIg in those patients in whom there is an index of suspicion for an immune-mediated motor neuropathy. However, IVIg is costly, may be in short supply, and may produce significant side effects. A previous report of 31 patients proposed a set of criteria by which a high likelihood of response to IVIg could have been predicted based upon a clinical examination, a CSF examination, and an assessment for proximal conduction block.⁴ If two of three were present, then there was a

95% chance that the patient would respond to IVIg. Perhaps the authors have these data.

CB often manifests motor weakness out of proportion to atrophy whereas axon loss should manifest as weakness with proportional atrophy. The authors comment on muscle atrophy but they did not specifically comment upon this relationship. Did all their patients manifest motor weakness out of proportion to bulk and tone in affected muscles with an MRC grade > 3? Furthermore, did these patients manifest needle EMG recruitment patterns suggestive of demyelination wherein there was early recruitment of very few units that had an increased firing frequency?

Delmont et al. admit that they did not perform additional studies that may have identified proximal conduction block. However, they did identify patients with F waves prolonged into the demyelinating range. Abnormal spontaneous activity with a normal cervical MRI would provide further support for their hypothesis of proximal conduction block with secondary axon loss at root

level. Did these authors examine the cervical paraspinal muscles in these patients in addition to obtaining a cervical spine MRI?

As albuminocytologic dissociation is uncommon in patients with motor neuronopathies, what percentage of patients in total had an elevated CSF protein? More specifically, what number of patients had at least one of the following: an examination suggestive of demyelination, inferred root level demyelination, and an elevated CSF protein? If all of Delmont et al.'s patients had at least one of these findings then perhaps treating neurologists should restrict empiric trials of IVIg to patients with lower motor neuron syndromes manifesting at least one of these criteria.

Daniel L. Menkes, *Memphis, TN*

The author reports no conflicts of interest.

Reply from the Authors: We thank Dr. Menkes for his thoughtful comments. We did not conclude that that IVIg treatment must be given to all patients with motor neuron diseases.¹ This treatment must be tested in selected patients presenting features of a multifocal motor neuropathy (MMN) whether conduction blocks are present or not.

Features suggestive of demyelination support the diagnosis of undetected conduction block. These criteria are clinical, biological, and electrophysiologic. Weakness in a peripheral nerve distribution and absence of bulbar, respiratory, and upper motor neuron involvement are suggestive of a MMN. The main biological criterion is a high titer of anti-GM1 antibody. Considering the nerve conduction study, delayed F waves latencies and delayed distal latencies suggest a demyelinating process even in absence of conduction block. Other techniques can be used to detect proximal conduction block, such as nerve root stimulation,⁴ conventional transcranial magnetic stimulation and triple stimulation technique,⁵ and brachial plexus MRI.⁶

Absence of muscle atrophy relatively to weakness is a good clinical sign of suspected demyelination, but it is a subjective evaluation without any quantitative data. A motor weakness with a peripheral nerve distribution on clinical and electrophysiologic examination is to us a more objective argument for a MMN rather than for a lower motor neuron syndrome. Elevated CSF protein is a good criterion of demyelination in CIDP. It is rare in MMN with conduction block and it is not a predictive factor of response to IVIg.⁷

We did not perform additional studies for proximal conduction block in this study,¹ but we did it in another study.⁵ Ten patients with motor neuropathies without conduction block had conventional transcranial magnetic stimulation and triple stimulation technique and, in seven patients, proximal conduction block was confirmed or temporal dispersion which was associated with a satisfactory response to IVIg. This technique is less painful and invasive than root stimulation.

Presence of conduction block is not required to treat patients with a typical pattern of motor weakness if a peripheral nerve distribution is present on clinical and electrophysiologic evaluation. The entity of MMN without CB is probably not a single entity based on our evaluation of proximal nerve segments by transcranial magnetic stimulation⁵ and based on our study¹ that did not find any significant difference between MMNs with CB and without CB.

E. Delmont, J.-P. Azulay, S. Attarian, A. Verschueren, D. Uzenot, J. Pouget, *Nice, France*

Disclosure: The authors report no conflicts of interest.

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References

1. Delmont E, Azulay JP, Giorgi R, et al. Multifocal motor neuropathy with and without conduction block: a single entity? *Neurology* 2006;67:592–596.
2. Chaudhry V, Swash M. Multifocal motor neuropathy: is conduction block essential? *Neurology* 2006;67:558–559.
3. Menkes DL. Axonal multifocal motor neuropathy without conduction block or other features of demyelination. *Neurology* 2002;59:1666.
4. Menkes DL, Hood DC, Ballesteros RA, Williams DA. Root stimulation aids in the detection of acquired demyelinating polyneuropathies. *Muscle Nerve* 1998;21:298–308.
5. Attarian S, Azulay JP, Verschueren A, Pouget J. Magnetic stimulation using a triple stimulation technique in patients with multifocal neuropathy without conduction block. *Muscle Nerve* 2005;32:710–714.
6. Van Es HW, Van den Berg LH, Franssen H. Magnetic resonance imaging of the brachial plexus in patients with multifocal motor neuropathy. *Neurology* 1997;48:1218–1224.
7. Van den Berg-Vos RM, Franssen H, Wokke JHJ, Van Es HW, Van den Berg LH. Multifocal motor neuropathy: diagnostic criteria that predict the response to immunoglobulin treatment. *Ann Neurol* 2000;48:919–926.

Prior TIA, lipid-lowering drug use, and physical activity decrease ischemic stroke severity

To the Editor: We read with interest the article by Deplanque et al. in which lipid-lowering drugs (LLDs) were shown to be associated with decreased stroke severity.¹ They concluded that this was likely due to the neuroprotective effects of these drugs.

We proposed another mechanism that may explain these findings: that hypercholesterolemia, by enhancing atherosclerosis and chronically compromising blood tissue supply, could trigger local compensatory mechanisms which ultimately reduce ischemia-induced tissue injury.² This may increase the brain's tolerance to sudden disruption of circulation and partially protect the tissue from acute ischemia.

High serum cholesterol levels are associated with less severe presentation and improved short-term functional outcome in stroke patients.³ Similar mechanisms may underlie the phenomenon of decreased stroke severity in smokers⁴ and of reduced myocardial injury following acute myocardial infarction in angina sufferers.⁵

It is reasonable to assume that patients taking LLDs were more likely to have been exposed to an extended period of hypercholesterolemia than those never treated with LLDs. The apparent benefit of taking LLDs prior to an ischemic stroke may partially reflect adaptive-protective mechanisms triggered by the preceding hypercholesterolemia rather than the neuroprotective effects of the drugs themselves.

It would be interesting to know the pretreatment cholesterol levels of the LLD-treated patients compared to the prestroke cholesterol levels of the untreated patients.

Marc Gotkine, Israel Steiner, *Jerusalem, Israel*

Disclosure: The authors report no conflicts of interest.

Reply from the Authors: We thank Drs. Gotkine and Steiner for their comments on our study.¹ We agree that aside from the potential neuroprotective effect of LLDs in stroke, the mechanisms involved in the development of a brain tolerance to ischemia must be identified.

Several studies have discussed whether chronic hypercholesterolemia could induce such a protective effect.^{3,4} In Alzheimer disease, the results conflict; several studies suggest a deleterious effect of mid-life hypercholesterolemia, while late-life hypercholesterolemia might have some beneficial effects.⁶ According to the methodology used and delay between stroke onset and cholesterol measurements, the results vary, which leads to misinterpretation. Our study was not designed to answer this question so conclusions cannot be definitive. Nevertheless, there is a growing body of evidence supporting the hypothesis that brain can adapt to injuries such as cerebral ischemia.^{1,7}

Experimental studies on preconditioning have shown that various conditions can initiate reactions in cells and tissues that lead after some time to neuroprotection. Although transient ischemia is typical of preconditioning stimulus, ischemic tolerance could be induced by exposing brain to various endogenous and exogenous stimuli (hypoxia, oxidative stress, inflammatory cytokines, lipopolysaccharide, linolenic acid, anesthetics) that converge downstream on fundamental mechanisms that ultimately account for the protection. They are based on the enhancement of cell survival through the modulation of various cellular and molecular pathways including variations at gene level.⁷ Given these data, targeting mechanisms of cytoprotection is an important strategy for new therapeutic

approaches. Because physical activity and LLDs have previously been experimentally demonstrated as possible inducers of brain ischemic tolerance,^{8,9} our study suggests the possibility to develop a prophylactic neuroprotection in humans.¹

In addition to experimental studies examining brain ischemic tolerance pathways, both physical activity and LLDs should now be prospectively evaluated to determine whether they are effective to reduce the severity of brain ischemia. The question of whether the decreased severity of stroke in patients under LLDs is due to an increased brain tolerance induced by LLDs themselves or by a chronically compromised blood tissue supply as suggested by Drs. Gotkine and Steiner can only be solved by randomized controlled trials in patients with similar baseline cholesterol levels.

According to a recent presentation of results from the SPARCL trial, it seems that patients randomized in the statin arm have less severe recurrent strokes.¹⁰ The hypothesis of Drs. Gotkine and Steiner is then unlikely to play an important role.

D. Deplanque, I. Masse, C. Lefebvre, C. Libersa, D. Leys,
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Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes

To the Editor: The BENEFIT trial on patients with a first clinical event suggestive of multiple sclerosis (MS) (clinically isolated syndrome; CIS) showed a significantly lower rate of conversion to clinically definite MS (CDMS) in patients treated with interferon beta-1b vs patients receiving placebo. The authors conclude that treatment with interferon beta-1b should be considered as a therapeutic option in patients presenting with a first clinical event suggestive of MS.¹

A crucial inclusion criterion of the study was the presence of at least two T2 lesions on a brain MRI scan. However, we believe that the uncommonly high number of baseline T2 lesions on brain MRI of the patients included in this study may represent an important source of bias concerning the applicability of this study to everyday practice.

It is well established that patients with CIS with a higher T2 lesion load on baseline brain MRI are more likely to progress to CDMS. Previous studies on MR imaging in CIS reported median T2 lesion numbers of less than 10. In the optic neuritis treatment trial, including 351 patients, Beck et al. report a median lesion number of 0.² O'Riordan et al. found a median lesion number between two and three in their study on 81 patients with different types of CIS.³ For patients with two or more lesions, the median lesion number in these two studies was 5 (R.W. Beck, personal communication) and in the range of 4 to 10 lesions.³

The patients included in the BENEFIT trial had median lesion numbers of 17 (placebo) and 18 (interferon) on baseline MRI, and are therefore much more likely to progress to clinically definite MS than patients seen in everyday practice. Interestingly, the median lesion number in the two previous trials on interferon treatment in CIS were also much higher than could be expected: 13 in the CHAMPS⁴ and 26 (interferon)/22 (placebo) in the ETOMS trial.⁵

We believe that the patients included in the CIS interferon trials represent only a subgroup of patients with CIS characterized by a high number of T2 lesions, indicative of a more aggressive disease course. Therefore, the results of these studies cannot be extrapolated to all patients with CIS.

Marcus W. Koch, Jop P. Mostert, Joeke J. de Vries,
Jacques De Keyser, *Groningen, The Netherlands*

Disclosure: The authors report no conflicts of interest.

Reply from the Authors: Koch et al. address the issue of applicability of the findings of the Betaferon in Newly Emerging multiple sclerosis For Initial Treatment (BENEFIT) study to everyday

References

1. Deplanque D, Masse I, Lefebvre C, et al. Prior TIA, lipid-lowering drug use, and physical activity decrease ischemic stroke severity. *Neurology* 2006;67:1403–1410.
2. Steiner I, Biran I. Better outcome after stroke with higher serum cholesterol levels. *Neurology* 2000;55:1941–1942.
3. Vauthey C, de Freitas GR, van Melle G, Devuyst G, Bogousslavsky J. Better outcome after stroke with higher serum cholesterol levels. *Neurology* 2000;54:1944–1949.
4. Karepov VG, Hass Y, Borenstein NM, Korczyn AD. Smoking reduces stroke severity. *Neurology* 1998;50 (suppl 4):A113.
5. Anzai T, Yoshikawa T, Asakura Y, et al. Effect on short-term prognosis and left ventricular function of angina pectoris prior to first Q-wave anterior wall acute myocardial infarction. *Am J Cardiol* 1994;74:755–759.
6. Mielke MM, Zandi PP, Sjogren M, et al. High total cholesterol levels in late life associated with a reduced risk of dementia. *Neurology* 2005;64:1689–1695.
7. Gidday JM. Cerebral preconditioning and ischaemic tolerance. *Nat Rev Neurosci* 2006;7:437–448.
8. Endres M, Gertz K, Lindauer U, et al. Mechanisms of stroke protection by physical activity. *Ann Neurol* 2003;54:582–590.
9. Bordet R, Ouk T, Pétrault O, et al. PPAR: a new pharmacological target for neuroprotection in stroke and neurodegenerative diseases. *Biochem Soc Trans* 2006;34:1341–1346.
10. Goldstein LB, The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. The SPARCL trial: effect of statins on stroke severity. *Ann Neurol* 2006;60(S10):S85.

practice. They suggest that patients in our study had unusually high baseline numbers of T2 lesions, and that this put them at heightened risk of conversion to MS compared with natural course studies or the North American Optic Neuritis Treatment Trial (ONTT).⁶

They further state that the median T2 lesion number of 17 at baseline, as observed in BENEFIT patients, is considerably higher than in both the ONTT (which evaluated the effects of corticosteroids in ON) and the London natural history study of patients with CIS.⁷ Koch et al. conclude that BENEFIT patients had unusually aggressive disease and that the results of the BENEFIT study cannot be extrapolated to all patients with CIS.

As stated in our article, the BENEFIT study included patients with CIS with at least two clinically silent T2 lesions on the baseline MRI scan. Therefore, findings of this study can only apply to patients with MRI findings suggestive of MS.

Comparing lesion numbers found in BENEFIT with those found in the ONTT or in the London study is problematic for several reasons: 49% and 33%, respectively, of patients in the ONTT and London studies showed no abnormalities suggestive of MS in baseline brain MRIs.^{6,7} The difference in the inclusion criteria between these studies and those of the BENEFIT study contributes to the difference in lesion numbers. The ONTT recruited only patients presenting with ON, who in some regional studies have fewer MRI lesions than other patients with CIS.^{8,9} Lesion counts may also be influenced by differences in scanner field strength and slice thickness as well as variability in assessments performed by central evaluation centers.¹⁰

A more recent study using equipment better comparable to the standards in the BENEFIT study has reported 60% of patients with more than 10 lesions.¹¹ More importantly, as reported in our article, the BENEFIT study also found robust treatment effects of interferon beta-1b in patients with CIS with less subclinical disease dissemination (i.e., participants with fewer than nine T2 lesions).

Considering these issues, we are convinced that the results of the BENEFIT study are applicable in guiding a physician's decision on interferon-beta 1b-treatment in patients with CIS who have MRI evidence of subclinical disease dissemination (at least two clinically silent lesions on brain MRI).

L. Kappos, C.H. Polman, M.S. Freedman, G. Edan,
H.-P. Hartung, D.H. Miller, X. Montalban, F. Barkhof,
L. Bauer, C. Pohl, R. Sandbrink, for the BENEFIT Study Group,
Basel, Switzerland

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References

1. Kappos L, Polman CH, Freedman MS, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurology* 2006;67:1242–1249.
2. Beck RW, Trobe JD, Moke PS, et al. High- and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: experience of the optic neuritis treatment trial. *Arch Ophthalmol* 2003;121:944–949.
3. O'Riordan JI, Thompson AJ, Kingsley DP, et al. The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. *Brain* 1998;121:495–503.
4. Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. *N Engl J Med* 2000;343:898–904.
5. Comi G, Filippi M, Barkhof F, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. *Lancet* 2001;357:1576–1582.
6. Beck RW, Arrington J, Murtagh FR, et al. Brain magnetic resonance imaging in acute optic neuritis. Experience of the Optic Neuritis Study Group. *Arch Neurol* 1993;50:841–846.
7. O'Riordan JI, Thompson AJ, Kingsley DP, et al. The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. *Brain* 2001;124:1052–1053.
8. Tintore M, Rovira A, Rio J, et al. Is optic neuritis more benign than other first attacks in multiple sclerosis? *Ann Neurol* 2005;57:210–215.
9. Swanton JK, Fernando K, Dalton CM, et al. Is the frequency of abnormalities on magnetic resonance imaging in isolated optic neuritis related to the prevalence of multiple sclerosis? A global comparison. *J Neurol Neurosurg Psychiatry* 2006;77:1070–1072.
10. Schach S, Scholz M, Wolinsky JS, Kappos L. Pooled historical MRI data as a basis for research in multiple sclerosis—a statistical evaluation. *Mult Scler* 2006;12:1–8.
11. Tintore M, Rovira A, Rio J, et al. Baseline MRI predicts future attacks and disability in clinically isolated syndromes. *Neurology* 2006;67:968–972.

Neurosurgery in Parkinson disease: A distressed mind in a repaired body?

To the Editor: Schüpbach et al. demonstrated discrepancy between motor and social impact of subthalamic stimulation (STN DBS) on patients with Parkinson disease (PD). While motor symptoms improved, social adaptation remained unsolved, with new conflicts and life problems.¹

During the past 7 years, we have treated 74 patients with PD bilaterally with STN DBS. We have never encountered social, marital, or professional troubles. After a mean of 34.2 months after surgery, sole STN DBS provided a 63.5% improvement of the general motor function. Clinical complications decreased by 86% when compared to preoperative condition.

Twelve of our patients retired before surgery because of PD and were still age-fit for work and 6 (50%) resumed full-time work after surgery. Of the total series, 4 patients were transferred to part-time positions or were about to quit work because of PD. All resumed full-time work responsibilities after surgery. Twenty-two (except one patient) maintained full active professional status.

Of the seven single patients, one got married after surgery. One familial conflict was noted in the family of a juvenile patient with PD. One patient from the Arab Gulf with newly developed hypomania and hypersexuality became temporarily separated from his wife. These problems were effectively managed by adjusting stimulation parameters and neuroleptics. A European patient, living abroad, got divorced and remarried.

Interestingly, most of the negative incidences we encountered were in our juvenile population (15%). Despite regular personal outreach interventions adopted for all our patients with PD, this population did not respond well.

After surgery, 7 patients (10.81%) were dissatisfied because of the persistence or new onset of moderate or severe axial symptoms because of the discrepant response of peripheral and axial PD symptoms to treatment. Interestingly, patients and their relatives developed this reaction despite careful preoperative instructions about prognosis, surgical outcome, and re-channeling of expectations into realistic endpoints.

Is the distressed mind observed in Schüpbach et al.'s article more frequent in Western societies? Is it common in the younger population? Are problems more frequent in patients undergoing late surgery? Could the social culture in our region, the outreach paraclinical and psychological support, or the 24/7 hotline service we provide be responsible for such favorable outcomes?

Further studies are needed to understand genuine DBS socio-medical impact.

Mazen G. Jabre, PharmD, Boulos-Paul W. Bejjani, MD,
Byblos/Jbail-Lebanon

Disclosure: The authors report no conflicts of interest.

Reply from the Authors: We thank Drs. Jabre and Bejjani for their letter describing psychosocial aspects among their patients with PD and subthalamic stimulation. Their observation that social adjustment is mostly unproblematic in their patients is interesting.

Differences in outcome cannot be explained by different methods of electrode implantation because targeting and surgical technique is the same in Byblos as in our center.² In addition, the motor improvement is excellent in both patient groups.

Four possible explanations for the discrepancies between their experience and the results from our study can be considered.¹

First, the accessibility of psychological support with a 24/7 hotline may contribute to better psychosocial outcome in Lebanese patients. While we do provide qualified psychological support, it is not possible to have the same accessibility and constancy of staff as their center because our patient load (250 patients since 1996) is heavier.

Second, the difficulties in psychosocial adjustment in our cohort became apparent only in a prospective trial with in-depth interviews with patients and their caregivers. We believe that some conflicts may not be revealed to physicians without specific exploration.

Third, the social security system has an impact on the efforts of patients to pursue a professional activity. There are important

differences between the French and Lebanese society that may explain some of the differences in outcome.

Fourth, the decisive factor for social adjustment is most likely the structure of the society in which the patient lives that define a person's role in the family, at work, and in society according to gender, age, and profession. For example, whereas divorce is very common in Western societies, it is still taboo in others. Divorce and failure to resume work after STN surgery does not necessarily equal worse psychosocial function. It may enhance quality of life, as observed in some of our patients.

In conclusion, as illustrated by these different results from two centers with similar treatment approaches, the structure and values of a society are pivotal for the psychosocial health of a given population. To enhance psychosocial health is a task that goes far beyond medical care.

Y. Agid, M. Schüpbach, M. Gargiulo, M.-L. Welter, L. Mallet, C. Behar, J.-L. Houeto, D. Maltête, V. Mesnage, *Paris, France*

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References

1. Schüpbach M, Gargiulo M, Welter ML, et al. Neurosurgery in Parkinson disease: A distressed mind in a repaired body? *Neurology* 2006;66:1811–1816.
2. Bejjani BP, Dormont D, Pidoux B, et al. Bilateral subthalamic stimulation for Parkinson's disease by using three-dimensional stereotactic magnetic resonance imaging and electrophysiological guidance. *J Neurosurg* 2000;92:615–625.

Correction

Intracerebral hemorrhage in pregnancy: Frequency, risk factors, and outcome

The study described in the article "Intracerebral hemorrhage in pregnancy: Frequency, risk factors, and outcome" (*Neurology* 2006;67:424–429) by B.T. Bateman et al. is an analysis of the Nationwide Inpatient Sample, a large, publicly available dataset that is maintained by the Agency for Healthcare Research and Quality (AHRQ). One of the provisions of the Data Use Agreement (DUA), which the authors signed when purchasing the dataset, is that no cross-tabulated data observation involving less than or equal to 10 patients is to be published. This measure was put in place by AHRQ to protect the privacy of individual patients and to prevent the potential disclosure of personal information. In the article there are a few observations which are in violation of this provision. This represents an oversight on the authors' part and an inadvertent failure to comply with the DUA. For this, the authors apologize. They note that while they are fully confident that nothing in the paper could be used to identify individuals or personal information, nonetheless the disclosures are in violation of the AHRQ guidelines. The authors have therefore asked the editors of *Neurology* to mark out the data cells that are in violation in the online version of paper and have requested that going forward authors cite only the corrected version of this manuscript. The corrected version of this article was posted at www.neurology.org on March 5, 2007.

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Correction

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