

and block tapping test). In addition, supratentorial hypoperfusion<sup>3</sup> was always detected.

We propose that our patient's cognitive deficits were the consequence of his cerebellar lesion. Several studies showed that the posterior or superior cerebellum may be involved in higher cognitive functions,<sup>1,2,8-10</sup> but few data are available about a cognitive role of the anterior portion of the cerebellum. In frontal lobe lesions, PET scans usually show a contralateral cerebellar hypometabolism. Conversely, in some infratentorial lesions, PET and SPECT scans showed hypometabolism/hypoperfusion in the contralateral cerebral hemisphere.<sup>1</sup> This reciprocal effect can be anatomically explained through the known cerebrocerebellar circuits. These consist in a feedforward loop, the cortico-ponto-cerebellar pathway, and a feedback loop, the cerebello-thalamo-cortical pathway.<sup>1</sup> In addition to its main projections to the sensorimotor cortex, the feedback loop also projects to some associative areas.<sup>8</sup> Most neuropsychological deficits occurring in patients with infratentorial lesion are explained by a diaschisis effect resulting in a defective activation of these areas.

In our patient, despite the presence of important cognitive abnormalities, we were not able to detect any significant hypometabolism/hypoperfusion in supratentorial regions, indicating that no diaschisis effect occurred, at least in its typical form. Also, the potential relative hypometabolism of a portion of his cingulate cortex cannot explain the extent of the observed neuropsychological deficits. Further functional imaging studies are necessary to define how lesions in different infratentorial areas of the cerebellum may alter functional connectivity between brain regions involved in cognitive tasks.

This case provides evidence of a direct involve-

ment of the cerebellum in some cognitive functions, agreeing with findings of cerebellar activation during cognitive processing in normal subjects.<sup>9</sup> A threshold effect may explain the variable effect of infratentorial lesions on cognition. Thus, bilateral anterior lesions, as observed in our patient, may be required to produce significant cognitive abnormalities.<sup>1,2</sup>

## References

1. Daum I, Ackermann H. Neuropsychological abnormalities in cerebellar syndromes—fact or fiction? *International Review of Neurobiology* 1997;41:455–471.
2. Neau JP, Arroyo-Anllo E, Bonnaud V, Ingrand P, Gil R. Neuropsychological disturbances in cerebellar infarcts. *Acta Neurol Scand* 2000;102:363–370.
3. Hoffmann M, Watts A. Cognitive dysfunction in isolated brainstem stroke: a neuropsychological and SPECT study. *Journal of Stroke and Cerebrovasc Dis* 1998;7:24–31.
4. Signorini M, Paulesu E, Friston K, et al. Rapid assessment of regional cerebral metabolic abnormalities in single subjects with quantitative and non-quantitative [18F]FDG PET: A clinical validation of statistical parametric mapping. *Neuroimage* 1999;9:63–80.
5. Van Bogaert P, Massager N, Tugendhaft P, et al. Statistical parametric mapping of regional glucose metabolism in mesial temporal lobe epilepsy. *Neuroimage* 2000;12:129–138.
6. Leber WR, Jenkins RL, Parsons OA. Recovery of visual-spatial learning and memory in chronic alcoholics. *J Clin Psychol* 1981;37:192–197.
7. Adams KM, Gilman S, Koeppe RA, et al. Neuropsychological deficits are correlated with frontal hypometabolism in positron emission tomography studies of older alcoholic patients. *Alcohol Clin Exp Res* 1993;17:205–210.
8. Middleton FA, Strick PL. Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. *Science* 1994;266:458–461.
9. Middleton FA, Strick PL. Cerebellar output channels. *International Review of Neurobiology* 1997;41:61–82.
10. Kim SG, Ugurbil K, Strick PL. Activation of a cerebellar output nucleus during cognitive processing. *Science* 1994;265:949–951.

## Midbrain deafness with normal brainstem auditory evoked potentials

**Abstract**—The authors report two cases of patients with word deafness. The word deafness occurred after a head injury for the first patient and after an arterio venous malformation embolization for the second patient. MRI demonstrated bilateral lesions of the inferior colliculi but brainstem auditory-evoked potentials (BAEP) were within normal limits. These cases demonstrated that lesions involving the two inferior colliculi induced pure word deafness but do not affect BAEP.

NEUROLOGY 2002;58:970–973

E. Vitte, MD, PhD; F. Tankéré, MD; I. Bernat, MD; A. Zouaoui, MD, PhD; G. Lamas, MD; and J. Soudant, MD

Pure midbrain bilateral and roughly symmetric lesion is a rare cause of total deafness. Because the auditory pathway is composed of crossed and uncrossed fibers

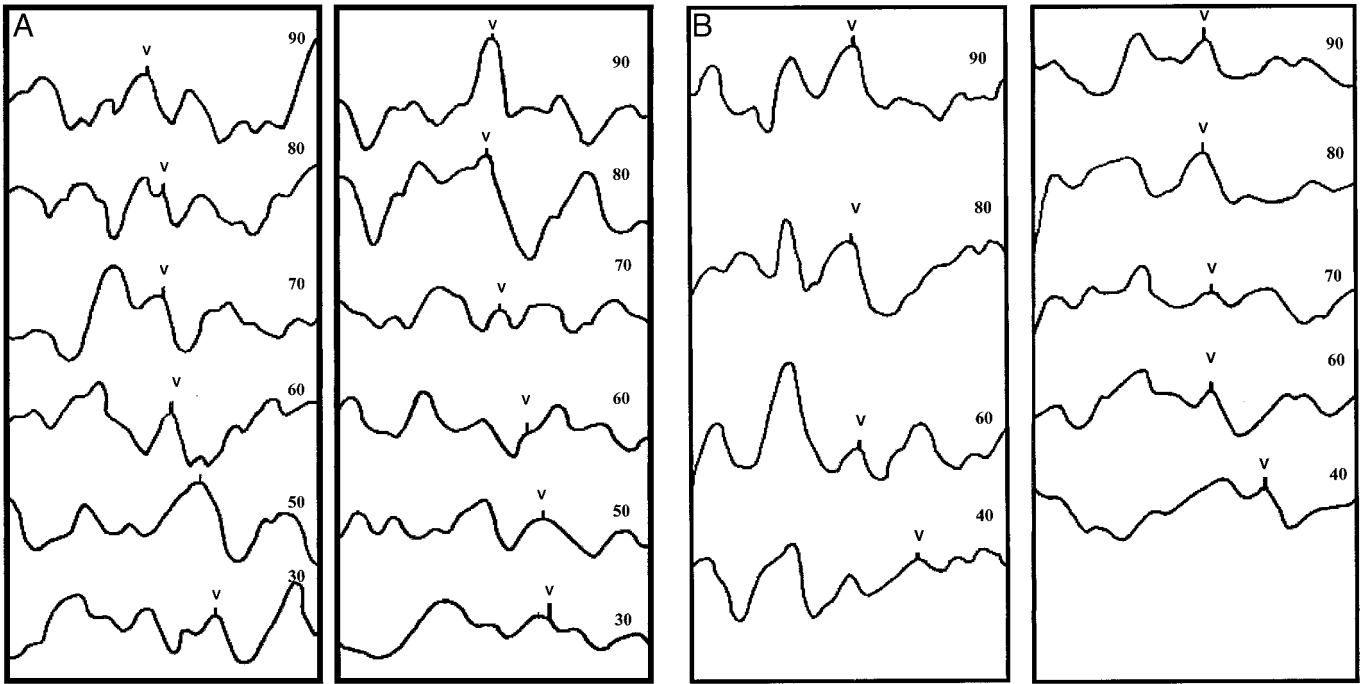
with multiple synapses in the brainstem and reach through the auditory radiations and the auditory temporal cortex, this pathway needs to be totally disrupted to induce a total deafness. We report two cases with bilateral symmetric lesions of the inferior colliculi. The patients had total deafness but their brainstem auditory-evoked potentials (BAEP) were within normal limits.

**Case report.** *Case 1.* A 57-year-old right-handed woman was seen at the ENT department of Pitié-

From the ENT Department (Drs. Vitte, Tankéré, Bernat, Lamas, and Soudant), Hôpital Pitié-Salpêtrière, and the Radiological Department (Dr. Zouaoui), Hôpital Pitié-Salpêtrière, Paris, France.

Received April 25, 2001. Accepted in final form December 4, 2001.

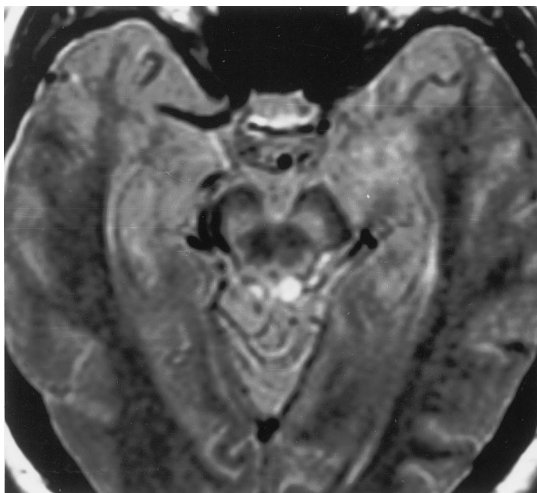
Address correspondence and reprint requests to Dr. Elizabeth Vitte, Service ORL (ENT Department), Hôpital Pitié-Salpêtrière, 83-91 Bld de l'Hôpital, 75013 Paris, France; e-mail: elizabeth.vitte@psl.ap-hp-hop-paris.fr



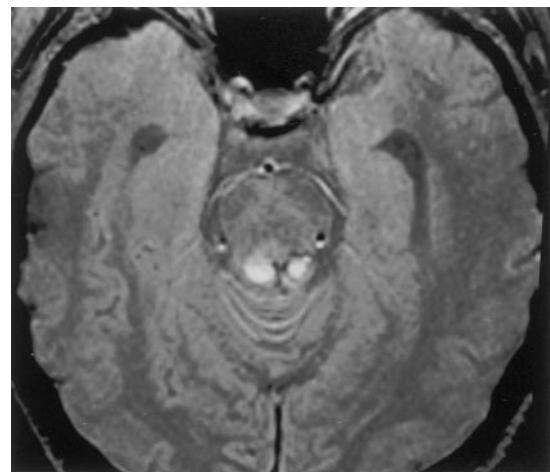
**Figure 1.** (A) Case 1. Surface-recorded brainstem auditory-evoked potentials (BAEP) to 38 dB (right side) and 56 dB (left side) normal hearing level (nHL) rarefaction clicks disclose waves I, III, and V. There was no increase of latencies of these waves on either side. Wave V was well preserved, with threshold of stimulation at 30dB nHL on both sides. (B) Case 2. Surface-recorded BAEP to 53 dB (right side) and 30 dB (left side). Wave V was well preserved, with threshold of stimulation at 40dB nHL on both sides.

Salpêtrière Hospital, Paris, 15 days after a head injury. She was disoriented and could speak, read, and write, but was unable to hear. There was no evidence of a thought disorder. Her history included losing consciousness during a motor vehicle accident induced by a high blood alcohol level. Standard pure tone audiometry demonstrated a mild bilateral sensorineural hearing loss of 38 dB for the right side and 56 dB for the left side. Impedance-audiometry revealed normal middle ear pressure and mobility bilaterally. The crossed and uncrossed stapedial reflexes were well preserved bilaterally. The acoustic reflex threshold

was 100 dB hearing level for 500, 1000, 2000, and 4000 Hz, suggesting that the middle and inner ear and the auditory nerve were intact. Speech audiometry failed to reveal any response. BAEP were normal (figure 1A). The absolute latencies for waves I, II, and V and the interwave latencies I-III and I-V were subjects at 70 dB on both sides. In so far as objective audiometry was normal while subjective audiometry was abnormal, her deafness was considered to be psychological. She was submitted to a cerebral MRI. A lesion localized to the tectum of the mesencephalon and involving the two inferior colliculi was found. This lesion



**Figure 2.** Case 1. MRI, axial T2-weighted sequence, lesion involving the tectum of the mesencephalon mostly on the left side.



**Figure 3.** Case 2. MRI, axial flow attenuated inversion recovery sequence, infarction of the tectum of the mesencephalon.

was hyperintense on T1- and T2-weighted sequences, suggesting a hemorrhage (figure 2). She was treated with bolus of steroids (1 g in a 1-hour perfusion of isotonic glucose) 3 times for the first week and once a month for 6 months. After 18 months, there was a recovery of the speech discrimination, which allowed the patient to wear hearing aids.

**Case 2.** A 52-year-old right-handed man was seen at the ENT department of Pitié-Salpêtrière Hospital, Paris, 2 days after an embolization of a diencephalic arterio venous malformation that had induced a venous infarction of the two inferior colliculi. He had a mild bilateral sensorineural hearing loss of 53 dB for the right side and 30 dB for the left side. Impedance-audiometry revealed normal middle ear pressure and mobility bilaterally. The crossed and uncrossed stapedial reflexes were normal (acoustic reflex threshold: 100 dB for all the frequencies tested); the BAEP were also normal (see figure 1B). No responses were recorded during the speech audiometry. MRI showed two well-limited hyperintense lesions involving the two inferior colliculi and suggesting an infarction (figure 3). The patient was treated with a protocol including perfusions of steroids and an agonist of dopamine (Piribedil; Euthérapie, Nevelly, France) for 1 week, followed by oral treatment for 2 months. Three months later, the speech discrimination was 100% bilaterally.

**Discussion.** The auditory pathway is composed of four neuronal networks. After passing through the external and middle ear, the sound reaches the inner ear where sensory transduction occurs. There is a tonotopy in the inner ear with fibers of the apex of the cochlea primarily responsive to low-frequency sounds. Hair cells of the cochlea are connected to type I auditory nerve fibers representing 95% of all nerve fibers. The auditory nerve enters the brainstem at the pontomedullary junction and each type I fiber terminates by splitting in two branches, one for each of the cochlea nuclei.<sup>1</sup> These fibers ascend as the lateral lemniscus in the brainstem. Fibers from the dorsal cochlear nucleus are projecting to the contralateral inferior colliculus. Fibers from the ventral cochlear nucleus have multiple bilateral projections including the trapezoid body, the superior olivary complex bilaterally, and both bilateral lemnisci and the inferior colliculi. The projections from the inferior colliculi terminate in the medial geniculate body and give rise to geniculate-temporal fibers (auditory radiations) that end in lamina IV of the primary auditory cortex (area 41, gyrus of Heschl).<sup>2</sup> This cortex is surrounded by association cortices.

The blood supply of all of these pathways is coming from the vertebral-basilar system. Branches from the posterior cerebral artery supply the inferior colliculi while branches coming from the middle cerebral artery supply the auditory cortex.

BEAP consist of 7 waves occurring within 10 milliseconds after the onset of the click stimuli. Wave I reflects mainly activity in the auditory nerve, wave III projections in the inferior olivary complex, and wave V the contralateral lateral lemniscus terminat-

ing in the inferior colliculus or the inferior colliculus itself.<sup>3,4</sup>

The neural generators of BAEP in humans are not completely known. Attempts to identify the anatomic locations of neural generators of the human BAEP based on the results of animal's studies commonly used in auditory experimentation have been difficult because of the considerable differences between the ascending auditory pathways in humans and animals.

Correlations between CT lesion sites and selective abolition of BAEP wave V or IV-V complex were made with patients who had midbrain-pontine hemorrhages or tumors.<sup>5</sup> Wave IV and V were consistently abolished by lesions involving the dorsolateral tegmentum of the midbrain-pontine junction area and the upper pons. These waves were not affected by lesions involving the inferior colliculus. It has been concluded that intact dorsolateral area of the upper pons is a prerequisite for waves IV and V to occur. Also, it has been suggested a medial auditory extralemniscal pathway.<sup>6</sup>

In the inferior colliculi, neurons are filters for sounds that require immediate action; neural processing is species-specific.<sup>7</sup> Components with latencies in the range of peak V elicited by contralateral click stimulation had their largest amplitudes when recorded from the lateral brainstem at the level of the trochlear nerve.<sup>4</sup>

Our two cases are examples of bilateral inferior colliculus lesions and total clinical deafness *but with preservation of wave V on BAEP recordings*. MRI abnormalities provide objective anatomic evidence for the organicity of the deafness. For the first case, contusion along the posterolateral aspect of the midbrain after head injury might be because of direct contusion by adjacent structures such as the free edge of the cerebellar tentorium. The second case is related to an infarction of the two inferior colliculi, probably of iatrogenic venous origin.

If wave V was generated by the inferior colliculus, our two patients should demonstrate a distortion or an abolition of wave V, but even for the lower intensity, wave V developed constantly. To our knowledge, three similar cases have been reported.<sup>8-10</sup> This suggests that wave V is not generated by the inferior colliculus but in a region caudal to the inferior colliculi and may be in the dorsolateral area of the upper pons, which is consistent with the abolition of waves IV and V in lesions affecting this area.

#### Acknowledgment

The authors thank Dr. Nadine Martin-Duverneuil for providing figure 2.

#### References

1. Häusler R, Levine RA. Auditory dysfunction in stroke. *Acta Otolaryngol* 2000;120:689-703.
2. Diamond IT, Feldman M, Galambos R, Goldberg JM. Neuroanatomy of the auditory system: report on workshop. *Arch Otolaryngol Head Neck Surg* 1973;98:397-413.
3. Melcher J, Kiang N. Generators of the brainstem auditory

- potentials in cat. III: Identified cell population. *Hear Res* 1996;93:52–71.
4. Moller AR, Jho HD, Yokoda M, Janetta PJ. Contribution from crossed and uncrossed brainstem structures to the brainstem auditory evoked potentials: a study in humans. *Laryngoscope* 1995;105:596–605.
  5. Chu NS. Brainstem auditory evoked potentials: correlation between CT midbrain-pontine lesion sites and abolition of wave V or the IV-V complex. *J Neurol Sci* 1989;91:165–177.
  6. Hinman CL, Buchwald JS. Depth evoked potential and single unit correlates of vertex midlatency auditory evoked responses. *Brain Res* 1983;264:57–67.
  7. Casseday JH, Covey E. A neuroethological theory of the oper-

- ation of the inferior colliculus. *Brain Behav Evol* 1996;47:311–336.
8. Hu CJ, Chan KY, Lin TJ, Hsiao SH, Chang YM, Sung SM. Traumatic brainstem deafness with normal brainstem auditory evoked potentials. *Neurology* 1997;48:1448–1451.
  9. Meyer B, Kral T, Zentner J. Pure tone deafness after resection of a tectal plate glioma with preservation of wave V of brainstem auditory evoked potentials. *J Neurol Neurosurg Psychiatry* 1996;61:423–424.
  10. Masuda S, Takeuchi K, Tsuruoka H, Ukai K, Sakakura Y. Word deafness after resection of a pineal body tumor in the presence of normal wave latencies of the auditory brain stem response. *Ann Otol Rhinol Laryngol* 2000;109:1107–1112.

## HLA-A2 homozygosity but not heterozygosity is associated with Alzheimer disease

**Abstract**—AD is associated with the A2 allele of the human leukocyte antigen (HLA). However, it is not currently known whether there is any difference between A2 homozygotes and A2 heterozygotes. The authors studied 458 patients with AD and found that A2 homozygotes had earlier onset of AD than either A2 heterozygotes (5.4 years,  $p = 0.002$ ) or those without A2 (5.2 years,  $p = 0.003$ ). The “recessive” nature of this association suggests that loss of function at the HLA-A locus or a closely linked gene is associated with AD.

NEUROLOGY 2002;58:973–975

S. Zarepari, PhD; D.M. James, BS; J.A. Kaye, MD; T.D. Bird, MD; G.D. Schellenberg, PhD; and H. Payami, PhD

AD, the most common neurodegenerative disorder, is genetically heterogeneous. The common form of AD, which includes sporadic early-onset AD and late-onset AD, is associated with the apolipoprotein E (*APOE*) gene.<sup>1</sup> *APOE-ε4* allele is associated with increased risk and earlier onset of AD, whereas *APOE-ε2* allele is associated with decreased risk and delayed onset. However, *APOE-ε4* is neither sufficient nor necessary for development of AD. Additional genes are suspected to contribute to the development of AD. Thus, many studies have examined the role of various genes on AD susceptibility.

Several studies have reported an increased frequency of human leukocyte antigen (HLA)-A2 allele in patients with early-onset AD (reviewed by Payami et al.<sup>2</sup> and Harris et al.<sup>3</sup>). A recent meta-analysis reported that the presence of one or more HLA-A2

alleles is associated with a modest increase in risk for developing AD.<sup>3</sup> Furthermore, one study examined the effect of HLA-A2 allele on age at onset of AD.<sup>4</sup> They observed that patients with AD with an HLA-A2 allele had an average 3 years earlier onset of AD than patients without A2. The association between the HLA-A2 allele and earlier onset of AD was confirmed by subsequent studies in Spain and Italy.<sup>5,6</sup> In addition, evidence for linkage to two regions on chromosome 6 has been detected in a genome scan of late-onset families.<sup>7</sup> However, the question of HLA-A2 allele dosage and a possible differential effect of A2 homozygosity compared with A2 heterozygosity has not been addressed. Thus, the goal of this study was to investigate the effect of HLA-A2 dosage on age at onset of AD in a sample of 458 unrelated patients with AD.

**Patients and methods.** This study was composed of 458 unrelated patients with AD (255 women and 203 men). All patients received the clinical diagnosis of probable AD or the neuropathologic diagnosis of definite AD as described previously.<sup>4</sup> Informed consent was obtained from every subject or from their legal guardian. Positive family history was defined as having a first-degree relative with AD or progressive memory loss (familial AD = 330, sporadic AD = 113, unknown family history = 15). Age at onset was defined as the age when memory loss was first noticed by relatives. Mean onset age ( $\pm$ SD) was  $68.0 \pm 10.1$  years.

HLA-A genotypes were obtained using a commercially available kit, the Olerup SSP HLA-A SSP Combi Tray (GenoVision, West Chester, PA). *APOE* genotypes were

From the Department of Neurology (Drs. Zarepari, Kaye, and Payami, and D.M. James), Oregon Health Sciences University; Portland Veterans Affairs Medical Center (Dr. Kaye) Portland, OR; Department of Neurology (Drs. Bird and Schellenberg), and Department of Medicine and Pharmacology (Dr. Schellenberg), University of Washington; Veterans Affairs Puget Sound Health Care System (Drs. Bird and Schellenberg), Seattle, WA.

Supported by the Indiana Alzheimer Disease Center National Cell Repository, NIAA grant #P30 AG 10133, and by grants from the Alzheimer's Research Alliance of Oregon, Alzheimer's Association (RG1-96-042), National Institute on Aging (AG-08017), Seattle Veterans Affairs Geriatric Research Education and Clinical Center, and University of Washington Alzheimer's Disease Research Center (NIA-AG05136).

Received October 25, 2001. Accepted in final form December 4, 2001.

Address correspondence and reprint requests to Dr. Sepideh Zarepari, Oregon Health Sciences University, 3181 SW Sam Jackson Park Road, CR-131, Portland, OR 97201; e-mail: zarepari@ohsu.edu

# Neurology<sup>®</sup>

## Midbrain deafness with normal brainstem auditory evoked potentials

E. Vitte, F. Tankéré, I. Bernat, et al.

*Neurology* 2002;58:970-973

DOI 10.1212/WNL.58.6.970

**This information is current as of March 26, 2002**

<b>Updated Information &amp; Services</b>	including high resolution figures, can be found at: <a href="http://www.neurology.org/content/58/6/970.full.html">http://www.neurology.org/content/58/6/970.full.html</a>
<b>References</b>	This article cites 10 articles, 2 of which you can access for free at: <a href="http://www.neurology.org/content/58/6/970.full.html##ref-list-1">http://www.neurology.org/content/58/6/970.full.html##ref-list-1</a>
<b>Citations</b>	This article has been cited by 3 HighWire-hosted articles: <a href="http://www.neurology.org/content/58/6/970.full.html##otherarticles">http://www.neurology.org/content/58/6/970.full.html##otherarticles</a>
<b>Subspecialty Collections</b>	This article, along with others on similar topics, appears in the following collection(s): <b>Audition</b> <a href="http://www.neurology.org/cgi/collection/audition">http://www.neurology.org/cgi/collection/audition</a> <b>Evoked Potentials/Auditory</b> <a href="http://www.neurology.org/cgi/collection/evoked_potentials-auditory">http://www.neurology.org/cgi/collection/evoked_potentials-auditory</a>
<b>Permissions &amp; Licensing</b>	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.neurology.org/misc/about.xhtml#permissions">http://www.neurology.org/misc/about.xhtml#permissions</a>
<b>Reprints</b>	Information about ordering reprints can be found online: <a href="http://www.neurology.org/misc/addir.xhtml#reprintsus">http://www.neurology.org/misc/addir.xhtml#reprintsus</a>

*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.

