

### The prevalence of migraine in neurologists

**To the Editor:** I was fascinated by Evans et al.'s article<sup>1</sup> but surprised to find no reference to Alvarez's 1960 article on the prevalence of migraine scotoma in physicians. He observed, in a group of 44 physicians, that no less than 87% had experienced "many solitary scotomata with never a headache," whereas in the general population (here he studied more than 600 patients) no more than 12% reported having experienced scotomata.<sup>2</sup>

Speculating on the possible reasons for the prevalence of migraine in neurologists, and particularly headache specialists, Evans et al. wonder, among other possibilities, whether "a personal history of migraines might stimulate an interest in neurology and headache as a subspecialty." For myself, with a personal history of classical migraines (and, more often, isolated visual ones) going back to childhood, the extraordinary phenomena of the aura (which for me included transient or partial achromatopsia, akinetopsia, as well as visual agnosias, alexias, etc.), excited an interest in the brain, and especially in visual processing, at an early age. These migraines were certainly one of the reasons I was attracted to neurology, why I chose migraine as the subject of my first book, and why I devoted a large part of this book to illustrating the varied presentations of visual auras in my patients.<sup>3</sup>

Oliver Sacks, MD, *New York, NY*

**Reply from the Authors:** We thank Dr. Sacks for his comments about our survey and the study by Alvarez.<sup>2</sup> Alvarez reports on 44 physicians with migraine interviewed at a medical convention. Eighty-seven percent had migraine aura without headache, a much higher proportion than reported by the neurologists in our

survey. In addition, of 618 migraineurs seen in his specialty practice, 12% of the men and 0.7% of the women reported scotomas without headache. In a large well-designed Danish study, Russell et al.<sup>4</sup> found a much lower lifetime prevalence of aura without headache (1% of males and 3% of females). The results of Alvarez are limited by the potential for selection bias and the lack of a well-specified case definition of migraine.

We were fascinated by Dr. Sacks' personal history of rare migraine auras leading to his interest in neurology. Although the burden of migraine and other headaches on employment is enormous,<sup>5</sup> this anecdote indicates an important previously unrecognized benefit. Although the prevalence of migraine is 66.6% among the authors of this publication (R.W.E. and S.D.S.), we believe that our career choices were independent of our personal medical histories.

Randolph W. Evans, MD, Richard B. Lipton, MD,  
Stephen D. Silberstein, MD, *Houston, TX*

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### Effect of antiepileptic drugs on bone density in ambulatory patients

**To the Editor:** The article by Farhat et al.<sup>1</sup> poses the following question: Do antiepileptic drugs (AED) and in particular chronicity of use give rise to an altered bone mineral density (BMD)? The use of the American database as a control group may flaw this study and invalidate the implication set out in the conclusion: that the differences found are due to antiepileptic medication. The population in Beirut is very different from the database and without first validating the database in Beirut we should be very cautious in suggesting that differences found relate to epilepsy or AED. Also, the authors found a significant correlation between duration of AED use and BMD. Was this corrected for age? If not, this alone could account for the difference.

Dougall J.P. McCorry, MRCP, MBChB, *Leeds, UK*

**Reply from the Author:** One of the primary endpoints chosen in our study is BMD, because it is a very powerful predictor of fracture risk as demonstrated in many cross-sectional and longitudinal studies from the United States and Europe. Although we have demonstrated in a population-based study that peak BMD is slightly lower in Lebanese compared to American subjects, we have warned against the use of the local database until validated.<sup>2</sup> It is for those reasons that we avoided the use of a local database in our study.<sup>1</sup>

First, the WHO definition of osteoporosis using BMD-derived T-scores only applies to Western Caucasian BMD databases,<sup>3</sup> the database in which the WHO T-score cutoffs were established, and the population in whom the BMD-fracture relationship is validated. No such validation is yet available in our population, and although we are in the process of conducting such study, until its results are available, the use of local databases would be flawed. Indeed, it is for these reasons that the International Osteoporosis Foundation (IOF) recommends the use of established universal databases.<sup>4</sup>

Second, it is reasonable to expect that the BMD-fracture relationship is the same in white patients whether they are American, European, or Lebanese. In fact, the IOF recommends the American NHANES III database as an international reference for hip T-score calculation and fracture risk estimates.<sup>4</sup> Furthermore, we

have demonstrated mean BMD in Lebanese and American patients with hip fractures to be very similar.<sup>5</sup>

Third, let us consider applying the approach suggested by McCorry to the cholesterol-coronary artery disease analogy in our population. Lebanese subjects have higher mean cholesterol level than Western counterparts. The argument presented by McCorry would imply that we should adjust the universally recognized NCEP cholesterol thresholds for intervention upwards taking into account local "normative databases." This would be unwarranted.

Contrary to what McCorry suggested, the inverse relationship in adults between BMD at the total body, total hip, and trochanter and duration of AED therapy is not due to age. The R values we reported between these variables varied between -0.38 and -0.45 and exceeded those known to correlate BMD and age, in the age range studied. In our study, the correlation between age and BMD was weaker and only significant at the trochanter. Finally, linear regression analyses revealed that duration of AED use, and not age, was a significant correlate of BMD at the three skeletal sites.

The results and conclusions presented in our study are solid and justified. However, as we discussed, the ultimate evidence for understanding the impact of epilepsy and AEDs on skeletal health will only be attained by conducting randomized trials.<sup>1</sup>

Ghada El-Hajj Fuleihan, MD, MPH, *Beirut, Lebanon*

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## Slowing Parkinson's disease progression: Recent dopamine agonist trials

**To the Editor:** The well-considered editorial<sup>1</sup> and two reviews<sup>2,3</sup> on therapeutic decisions in Parkinson's disease (PD) missed several points and some rationales are suspect.

Trials of pramipexole<sup>4</sup> and ropinirole<sup>5</sup> versus levodopa were discounted. The greater dyskinesias with levodopa were attributed to more aggressive treatment interpreted from differences on the Unified Parkinson Disease Rating Scale (UPDRS) motor scores. However, physicians were blinded and could not have utilized different criteria for adequate control. This is supported by the lack of significant difference in the UPDRS activities of daily living (ADL) scores. It is possible that the differences in the UPDRS motor scores were an artifact. Factor analysis demonstrated that certain symptom domains may have a disparate effect on the scores of the UPDRS motor scores.<sup>6</sup> Thus, a slight and perhaps clinically insignificant advantage of levodopa among these symptoms could skew the motor score.

Were differences in UPDRS motor scores sufficient to explain the differences in dyskinesia? From the published data,<sup>5</sup> 174 patients would have to be treated have a 90% chance of detecting a significant difference at the  $p < 0.05$  level (Stata, Stata Corporation, College Station, TX). Conversely, only 80 patients would have to be treated to see a significant difference in the prevalence of dyskinesias. Before the introduction of levodopa, only 49 patients would have to be treated.

The higher risks of short-term and lower efficacy of dopamine agonists were used as straw-man arguments. The reversible acute side effects are qualitatively different than potentially irreversible dyskinesias. For patients achieving adequate control on either medication, the dopamine agonists are just as efficacious as levodopa. Also, discounting the consequences of dyskinesia skews risk/benefit considerations.

Although not intentional, the lack of smoking gun evidence may give some the impression of immunity for any position. Alternative explanations are inexhaustible, thus providing limitless ammunition for radical skepticism resulting in therapeutic nihilism. Physicians are not expected to have all the answers but they are expected to use their best judgment. Whereas future research may change the available evidence, the needs of patients today compel the physician to make judgments today.

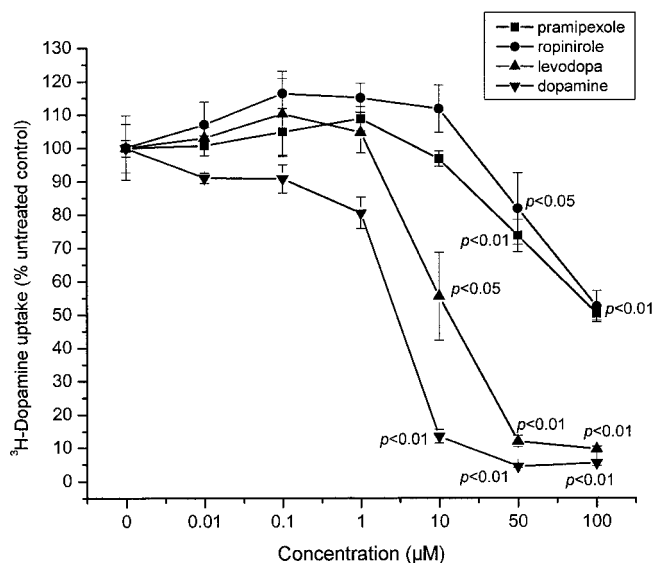
Finally, if it is the patient's or the patient's proxy's right to decide how the patient is treated, then our responsibilities are to present all sides reasonably. If so, the debate as to whether a physician should prescribe dopamine agonists or levodopa is misdirected.

Erwin B. Montgomery, MD, Cleveland, OH

**To the Editor:** In recent clinical trials, <sup>123</sup>I-β-CIT in SPECT and <sup>18</sup>F-dopa in PET showed less decline of imaged striatal dopaminergic signal in patients with PD following 2 to 4 years of treatment with pramipexole and ropinirole compared with levodopa.<sup>7,8</sup> The authors suggested that such decline of imaged striatal dopamine signal might reflect a slowed progression of PD, possibly due to neuroprotective effects of pramipexole and ropinirole. Ahlskog, however, analyzed the results of these clinical trials and proposed alternative interpretations.<sup>2</sup> He suggests that pramipexole may exert a pharmacologic regulatory influence on dopamine transporter (DAT) and ropinirole may reduce dopa influx and thus affect <sup>18</sup>F-dopa PET.<sup>2</sup> Although Ahlskog's concerns are very reasonable, sound scientific, pharmacologic data in support of his comments are lacking. We have, therefore, conducted *in vitro* experiments designed to explore the effects of pharmacologic regulation of pramipexole, ropinirole, levodopa, and dopamine on DAT uptake using human dopaminergic neuroblastoma SHSY-5Y cells.

We found that pramipexole and ropinirole, at concentrations of 0.1 to 1 μM, thought to be in the range of usual clinical doses,<sup>9</sup> had no significant effect on DAT uptake, whereas levodopa and dopamine at concentrations of 10 to 50 μM, comparable to the clinical doses, had significant inhibitory effect on DAT uptake (figure). Although there were significant inhibitory effects of pramipexole and ropinirole on the [<sup>3</sup>H]-dopamine uptake at concentrations of 50 to 100 μM, the magnitude of the inhibition was much less than that achieved with levodopa and dopamine, and the concentrations were probably not clinically relevant.

Our findings suggest that the pharmacologic effects of



**Figure.** Effects of pramipexole, ropinirole, levodopa, and dopamine on the <sup>3</sup>H-dopamine uptake in human dopaminergic neuroblastoma SHSY-5Y cells. After the incubation of pramipexole, ropinirole, levodopa, or dopamine with concentrations ranging from 0.01 μM to 100 μM in the presence and absence of dopamine transporter (DAT) inhibitor mazindol (10 μM) for 1 hour, the uptake was conducted at 37 °C for 10 min with 5 nM final concentration of [<sup>3</sup>H]-dopamine (0.21 μCi/mL). The difference between total uptake (in the absence of mazindol) and nonspecific uptake (in the presence of 10 μM mazindol) was defined as specific DAT-mediated uptake. Values shown represent the means ± SEM of at least three independent experiments, each performed in triplicate. Results were considered significant at 0.05 and very significant at 0.01 (one-way analysis of variance).

pramipexole or ropinirole on DAT uptake are minimal and probably do not account for the reported slowing of decline in striatal <sup>123</sup>I-β-CIT uptake.<sup>7,8</sup> Our findings also suggest that the decline in striatal <sup>123</sup>I-β-CIT uptake by levodopa, as demonstrated by the above studies and by the ELLDOPA trial,<sup>10</sup> may be in part attributed to the inhibitory effect of levodopa on DAT at the concentrations relevant to the clinical doses.

Our study, however, does not rule out the possible effects of these tested dopaminergic drugs on DAT phosphorylation, expression, turnover, and other pharmacologic effects. Further experiments, both *in vitro* and *in vivo*, are needed to differentiate between clinically relevant, disease-modifying, effects of these drugs and their direct effects on the surrogate markers that may help clarify the interpretation of the clinical studies.

Tianhong Pan, MD, PhD, Weidong Le, MD, PhD, Joseph Jankovic, MD, Houston, TX

**Reply from the Author:** Dr. Montgomery has raised a very interesting point regarding the pramipexole<sup>4</sup> and ropinirole<sup>5</sup> clinical trials: levodopa monotherapy was significantly more efficacious, despite liberal supplemental levodopa in the dopamine agonist arms. In fact, better efficacy with levodopa monotherapy was also found in two other dopamine agonist multicenter trials.<sup>11,12</sup> These results should not be an artifact of the UPDRS motor test battery because ADL scores tended to follow this same pattern. UPDRS ADL scores were superior in the levodopa arms in all three trials where reported. This was highly significant ( $p = 0.001$ ) in one,<sup>4</sup> with a similar, albeit nonsignificant trend ( $p = 0.08$ ) in another<sup>5</sup>; in the third study, the ADL scores were better in the levodopa arm but no statistical analyses were reported.<sup>11</sup>

How to explain this? Despite the double-blind study designs, it

is conceivable that treating physicians were able to sense the true identity of the study drugs from the patients' responses. If biased toward agonist therapy, they might have tended to limit the levodopa dosage in the dopamine agonist arms (resulting in fewer dyskinesias). However, it seems unlikely that investigators in all four trials would display such consistent bias.

I suggested an alternative explanation<sup>2</sup>: these findings are what one would predict if DAT was upregulated by dopamine agonist therapy. Greater expression of DAT per neuron should result in more effective clearance of dopamine from the synaptic region. This should result in fewer dyskinesias but a less robust antiparkinsonian response, which were the findings in all four clinical trials.<sup>4,5,11,12</sup> Similar regulatory changes in other proteins involved in dopamine transport, metabolism, and neurotransmission could also generate this outcome.

The phrase "potentially irreversible dyskinesias" deserves comment. Dyskinesias represent a short-duration response to a given levodopa dose. They resolve within a few hours and will totally abate with levodopa dose reduction; hence, they are not truly irreversible. The dyskinesia potential is related to the duration of PD and not simply to the duration of levodopa treatment.<sup>3,14</sup> Dyskinesias are rare early in treatment but with approximately 40% incidence by 5 years.<sup>14</sup> Among some of those affected, the dyskinesias will be limited and inconsequential. For others, the dyskinesias will be controlled by medication adjustments. Only a small minority of our patients displays the worst-case scenario that the term dyskinesias brings to mind: wild, generalized flailing chorea that only resolves with levodopa reduction to subtherapeutic levels. Perhaps dyskinesias should not be the primary factor in our early PD treatment decisions.

Finally, dopamine agonist monotherapy is not nearly as efficacious as levodopa. This is why only a very limited number of patients could be maintained on agonist monotherapy for more than a few years in any of the published clinical trials to date.

I am flattered that Pan et al. were prompted by my article<sup>2</sup> to address these issues in the laboratory. My expressed concerns relate to a fundamental premise of the CALM-PD and REAL-PET trials,<sup>7,8</sup> where the investigators assumed that the study drugs do not influence the regulation of proteins critical to the transport, binding, or metabolism of the imaging radioligands. The Pan et al. experiment does not address true regulatory effects associated with chronic PD drug treatment. Their acute results could be explained by pharmacologic competition at the DAT between [<sup>3</sup>H]-dopamine and the study drug in the incubation medium (levodopa or dopamine). Nonetheless, they are relevant to trials in which the study drugs are not withheld before imaging (unclear whether they were withheld in the CALM-PD study).<sup>7</sup>

Pan et al. mention that "sound scientific, pharmacologic data in support of" the concerns raised in my manuscript "are lacking." (Of course the same criticism may more appropriately be applied to the fundamental premise of the CALM-PD and REAL-PD trials<sup>7,8</sup>). The following conclusions, however, are supported by "sound scientific, pharmacologic data" (references previously cited).<sup>2</sup>

- DAT is a highly regulated protein and dopamine agonists and levodopa influence this regulation. For beta-CIT SPECT imaging to be a reliable biomarker of PD progression requires proof that study drugs are not simply affecting DAT expression, turnover, or function.
- <sup>18</sup>F-dopa metabolism is pharmacologically regulated and at more than one site. Both peripheral and central dopa decarboxylase are regulated proteins and striatal dopa decarboxylase is rate limiting. (Transporter proteins carrying <sup>18</sup>F-dopa across the blood-brain barrier and neuronal membranes may also be regulated and pharmacologically influenced but this has not been investigated.) The differential effects of chronic carbidopa/levodopa and dopamine agonist administration on <sup>18</sup>F-dopa/dopamine metabolism, transport, and turnover must be fully defined before we can employ this as a reliable biomarker of PD progression.

Pan et al. also cited the ELLDOPA study.<sup>10</sup> This is the third clinical drug trial in which the striatal dopamine imaging results were opposite to the clinical outcomes.<sup>7,8,10</sup> These discordant results require an explanation if we are to believe that these imaging studies are valid measures of PD progression.

J. Eric Ahlskog, PhD, MD, Rochester, MN

**Reply from the Editor:** Dr. Montgomery suggests that I attributed the higher incidence of dyskinesias with levodopa to "more aggressive treatment." He is incorrect. In the studies comparing pramipexole and ropinirole to levodopa, treating physicians were indeed blinded to drug treatment but were forced by protocol to use specific dosing increments of agonist or levodopa. The clear, significant findings in each study were that patients treated with levodopa showed greater improvement in motor UPDRS scores and a higher incidence of dyskinesias. I interpret these data as another evidence of better efficacy of levodopa, driven by the drug doses specified by the protocols, not more aggressive treatment.

Dr. Montgomery suggests that levodopa-induced dyskinesias are more "significant" than reversible acute side effects of agonists. Levodopa-induced dyskinesias subtend a spectrum of clinical significance and reversibility. On the other hand, "reversible acute side effects" of agonists are often not trivial and may preclude further use of the drug. For example, sedation with daytime somnolence caused by agonists is acute but usually not reversible unless the drug is discontinued. Thus, it is very difficult to make any useful conclusions about the significance of side effects.

I completely concur with Dr. Montgomery's homily in his fourth and final paragraphs.

G. Frederick Wooten, Charlottesville, VA

**Reply from the Authors:** Dr. Montgomery raises interesting points. We do not discount the results of the DA-levodopa comparator trials. These trials formed primary data for our analysis. Dr. Montgomery suggests that differences in intensity of treatment measured by the UPDRS motor scale could be an artifact. He suggests that lack of significant differences in the UPDRS ADL scale implies equivalent therapeutic effects. Actually, in the CALM-PD trial, there were significant differences favoring levodopa treatment in the UPDRS ADL scale.<sup>3</sup> The PD Research Group of the United Kingdom (PDRGUK) study comparing initial bromocriptine with levodopa therapy supports our interpretation.<sup>15</sup> This trial used a different disability assessment method and demonstrated a difference in favor of levodopa. Dr. Montgomery's point that the motor component of the UPDRS is driven by effects in limited domains is irrelevant. As long as those domains reflect clinically significant phenomena, the motor scale is useful. His power calculations are irrelevant also. If anything, they show that these studies would be relatively insensitive to detecting differences in treatment intensity, which may have biased study outcomes toward a result favoring initial DA treatment.

Dr. Montgomery's differentiation of "acute and reversible" versus "irreversible" side effects is not useful. Dyskinesias are no more or less reversible than hallucinations and so-called acute side effects are often more disabling than dyskinesias. Dr. Montgomery's suggestion that dyskinesias are qualitatively different from other side-effects ignores that fact that many patients with PD experience mild and insignificant dyskinesias. In the PDRGUK study, which has unparalleled follow-up, there was no difference in the incidence of moderate to severe dyskinesias.<sup>15</sup>

Dr. Montgomery errs in implying that we are extreme skeptics. Authentic extreme skepticism is an epistemologic stance precluding conclusions about any feature of human experience.<sup>16</sup> We are mitigated skeptics; reaching conclusions only after critical evaluation of data.<sup>16</sup>

Finally, debate about initial treatment of PD is appropriate and necessary. Patients do not have unlimited rights to decide how they are treated. The generally accepted formulation of medical ethics identifies four crucial principles: respect for autonomy, nonmaleficence, beneficence, and concern for justice.<sup>17</sup> Application of the last three principles involves paternalistic behavior. Dr. Montgomery's remark, which we doubt reflects his actual practice, implies priority for respect for autonomy. Beauchamp and Childress, however, specify that none of the basic principles have priority.<sup>17</sup> Assigning priority to autonomy is questionable philosophy and poor clinical practice.

Roger L. Albin, MD, Kirk A. Frey, Ann Arbor, MI



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## Pure dysarthria due to small cortical stroke

**To the Editor:** We read with interest the article by Kim et al.<sup>1</sup> concerning a series of six patients with pure dysarthria with or without other minimal neurologic signs due to small cortical strokes. Here we report two additional cases in which FLAIR and diffusion-weighted MRI (DWI) identified small cortical infarctions.

**Case 1:** A 63-year-old right-handed woman was admitted for sudden transient dysarthria with a minimal left central facial paresis that lasted approximately 10 hours. She had a history of arterial hypertension and breast cancer. She was on enalapril 10 mg/day and tamoxifen. The neurologic examination demonstrated moderate dysarthria with a mild left lower facial paresis without compromising tongue motility. Cervical doppler ultrasound, transesophageal echocardiogram, and brain CT scan had normal results. A brain MRI performed 24 hours after the onset of the neurologic symptoms showed a cortical lesion with hyperintense signal on FLAIR and proton density sequences involving the right precentral and the posterior edge of the middle frontal gyrus (figure 1, A and B).

**Case 2:** A 58-year-old right-handed man with a history of hypertension was admitted for an abrupt onset of dysarthria and paresthesias localized on the right side of his tongue and homolateral perioral area. Minutes later, mild weakness developed in his right hand. His neurologic examination evidenced moderate dysarthria, mild and distal paresis, and decreased pinprick sensation limited to his right first and second fingers. Tongue motility was normal. A brain MRI revealed two small cortical ischemic lesions that showed hyperintense signal in FLAIR and DWI sequences (figure 2, A and B). The first was located on the left knob hand area and compromised part of the anterior border of the postcentral gyrus. The second affected the posterior third of the left middle frontal gyrus. Brain and cervical MRI angiography had normal results.

Isolated dysarthria or dysarthria associated with other minimal neurologic deficits secondary to stroke with small cortical lesions are rare<sup>2</sup> and may not be identified by CT or conventional MRI.<sup>1</sup> In the current cases, they were identified only by proton density, FLAIR, or DWI. We hypothesized that in our patients the dysarthria could be secondary to compromise of the cortical areas related or connected to the corticobulbar tract.<sup>2</sup> In both cases the infarction was located in the posterior part of the middle frontal gyrus. In the first case, the dysarthria associated to mild left central facial paresis could suggest the involvement of the corticofacial tract that runs very close to the corticolingual fibers<sup>3</sup>; in the second, the dysarthria could be explained by the well-known association between pure dysarthria and cortical hypoperfusion in the medial prefrontal and premotor cortex.<sup>4</sup> The other lesion, located at the knob area, explains the finger movement disability.<sup>5</sup> These two additional cases contribute to highlight 1) DWI and proton density MRI sequence sensitivity in identifying small cortical lesions, 2) that an isolated cortical lesion can lead to dysarthria, and 3) the role of the middle frontal gyrus in the motor mechanisms of speech.

Emilia M. Gatto, MD, Claudia Uribe Roca, MD, María Cristina Zurrú, MD, Carlos A. Rugilo, MD, Buenos Aires, Argentina

**Reply from the Author:** I appreciate Gatto et al.'s interest in our article,<sup>1</sup> and found their cases interesting. It seems clear that DWI is more sensitive than T2-weighted MRI in detecting small cortical lesions. It reliably differentiates ischemic lesions from the CSF space. Although small cortical ischemic lesions producing pure or predominant dysarthria have been regarded as an uncommon occurrence previously,<sup>6,7</sup> this is not so in the era of DWI. However, the exact prevalence of pure cortical dysarthria requires large-scale, prospective studies.

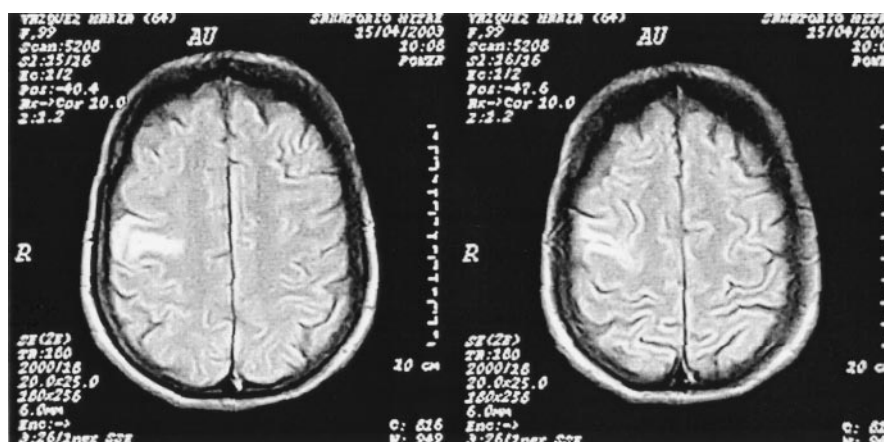


Figure 1. (A, B) FLAIR images (repetition time 8,000, echo time 180, inversion time 2,100) show hyperintense cortical lesions involving the precentral and the posterior part of the middle frontal gyrus of the right cerebral hemisphere.

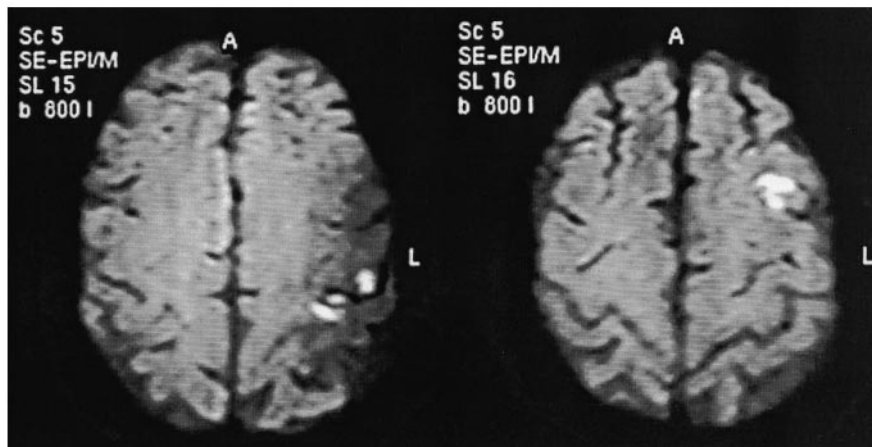


Figure 2. (A, B) Diffusion-weighted images (repetition time 1,600, b value 800) show small hyperintense cortical lesions involving parts of left knob hand area and anterior edge of the postcentral gyrus. Another lesion is evident in the posterior third of the left middle frontal gyrus.

Regarding Case 2 of Gatto et al., although previous authors reported decreased frontal blood flow in patients with dysarthria, the lesions were actually located bilaterally in subcortical areas. Therefore, I do not think that the lesion in the middle frontal gyrus produced dysarthria in this patient. It was probably caused by the lesion located just lateral to the precentral knob, which more adequately explains bulbar motor dysfunction.

Jong S. Kim, MD, Seoul, South Korea

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## Pure dysarthria due to small cortical stroke

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