

## Letters to the Editor Related to Published Articles

### Olfaction Testing in PD: Risky Conclusions

I read the article “Association of Olfactory Dysfunction with Incidental Lewy bodies (ILB)”<sup>1</sup> with interest. Recent studies state that hyposmia, REM sleep behavior disorder (RBD), and constipation antedate the appearance of motor symptoms and they can be early “premotor” markers of the disease (reviewed in Ref. 2). The issue is to determine their predictive value as to be applied as reliable screening tools.

Results of three prospective studies carried out in subjects suffering from hyposmia show that its predictive value (probability of developing parkinsonism in the long-run) ranges from 0% at time of death in this study<sup>1</sup> to 10% at two years in a study with relatives of patients with sporadic PD.<sup>3</sup> The design of the Honolulu-Asia Aging Study<sup>1</sup> is the most suitable one to establish the value of olfactory testing as a screening tool in general population. Its purpose was to determine the association of olfactory dysfunction during late life with Lewy bodies in the substantia nigra or locus ceruleus. 164 autopsied men without clinical PD or dementia had olfaction testing during one of the examinations. Ten of 17 with ILB had hyposmia. Thus, the possibility of having Lewy bodies was significantly increased in individuals with frank hyposmia. The problem arises with this statement: “*Olfactory testing may be a simple and economical way to identify an age-appropriate population at high risk for developing PD that could be enrolled in pharmaceutical trials aimed at preventing or slowing progression of PD*”. This conclusion is based on the assumption that a given individual with a reduction in olfaction will eventually develop parkinsonian motor or cognitive symptoms; otherwise, it is difficult to understand it. However, none of the examined octogenarian subjects showed parkinsonism during their lifetime! Evenmore, only 10 out of 55 individuals with a frank hyposmia showed nigral Lewy bodies (stage II–III of Braak). This proportion (18%) is considerably higher than that of individuals with normal olfaction (6.8%); however, its value as a screening tool in the general population seems to be quite limited. Likely, value will increase in carefully selected populations (patients’ relatives, nonsmokers, non-green tea or coffee drinkers, subjects with RBD or constipation, . . .) or by combining more than one test. However, this greatly constrains its potential applicability.

Misuse of these presumed biomarkers as predictors of “motor PD” could have serious ethical implications. How to explain the need of clinical follow-up or functional neuroimaging studies? I am convinced that this may have negative rather than positive effects. What about ethical implications? Is it ethical to try to identify “individuals at risk” if we cannot give any certain medical advice about their future? A solution to overcome ethical conflicts is to conduct a blind longitudinal study in

asymptomatic individuals with and without “premotor” abnormalities. This scenario is quite unrealistic.

PD is a multisystem disorder, but it does not necessarily follow a predefined order. Accordingly, the value of “premotor” symptoms as biomarkers would be quite limited. I recognize that the aim is of extraordinary importance but I am afraid that the starting point (PD seen as a continuum) is incorrect. And, please, remember that the prevalence of clinically significant PD is 1–2%.

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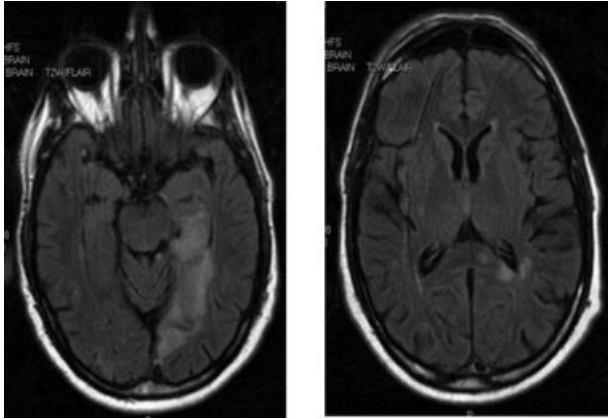
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### Dominant vs. Nondominant Posterior Alien Limb—Is it the Same Phenomenon?

We read with interest the article entitled “Alien limb following posterior cerebral artery stroke: Failure to recognize internally generated movements?” by Coulthard et al.<sup>1</sup> The authors proposed that the mechanism underlying the generation of “alien” movements in posterior parietal lesions requires the constellation of deficient proprioceptive and visual feedback from the moving limb together with loss of sense of motor intention and internal model of the current state of the arm. They showed that sensory loss and visual field defect or neglect were present in all right hemispheric lesion cases cited in the literature. We observed a



**FIG. 1.** Left: Axial T2 flair MR images obtained 6 days after admission demonstrating a hyperintense lesion compatible with an ischemic stroke in the territory of the posterior cerebral artery. Right: Ischemic lesions in the posterior corpus callosum and also adjacent to the left lateral ventricle.

patient with a right posterior alien hand syndrome with hemianopia, but only minor sensory loss due to a lesion of the dominant posterior parietal lobe and the splenium of corpus callosum. Mechanisms underlying the dominant hemispheric posterior alien hand might differ from those of the nondominant hemisphere, which necessarily present with neglect and significant proprioceptive sensory loss.

A 55-year-old right handed immunocompetent man presented with right limbs weakness and fever. He had been somnolent for the last 3 days. He had normal cardiac sounds, no signs of systemic infection. Neurological examination revealed dense right hemianaopia accompanied by mild right limb weakness. The muscle tone was normal, reflexes were brisk on the right limbs. The plantar response was extensor on the right. In addition, his right upper limb showed involuntary levitation.

Speech was fluent with normal comprehension and repetition. Naming was normal besides the ability to name colors.

When asked theoretically about common objects' colors, the patient gave correct answers, but was unable to name seen colored items. He demonstrated alexia without agraphia. Calculation and left-right orientation were preserved. He had no frontal signs (grasping or palmomental reflex).

The right upper limb demonstrated slow involuntary levitation movements, which consisted of elevation of the whole upper limb. He was aware of their existence but denied performing them voluntarily. When relocated at knee level, the hand was quiet, showing normal praxis and no groping activity. The right limbs showed mild hypoesthesia for touch and pinprick, but no proprioceptive loss. The right upper limb showed minimal cerebellar ataxia. No intermanual conflict, exploratory or self-mutilation behavior was present. The movements did not cause fear or anger.

Brain MR disclosed an acute infarction in the left posterior parietal, temporooccipital area, and splenium of the corpus callosum due to left posterior cerebral artery occlusion (see Figure 1). Bacterial endocarditis was diagnosed based on echocardiography, which demonstrated an aortic valve vegetation and *Streptococcus viridans* isolated in blood cultures. In the following days, body temperature returned to normal. The alien hand and focal signs disappeared after a week with residual upper right quadrantanopia.

Our patient exhibited a symptom constellation consistent with a posterior alien hand syndrome. This type is characterized by purposeless arm wandering and instances of levitation. "Denial of ownership" and purposeful movements seen the classical types are not required in the posterior type as in our patient. It was described with lesions of the posterior parietal lobe, corticobasal ganglionic degeneration<sup>2</sup> or Creutzfeldt-Jakob disease.<sup>3</sup> The posterior variant is rare, mainly described in nondominant hemispheric lesions.<sup>4</sup> Dominant hand involvement as in our patient is reportedly rare (Table 1). Coulthard et al. suggest that the posterior alien hand consequent to a combination of deficient motor intention and impoverished sensory representation of the contralesional limb. The proposed mechanism was damage to the internal model of the current state of the limb due to parietal lobe lesion. The authors found that all

**TABLE 1.** Clinical findings in patients with dominant posterior alien hand syndrome

Comments	Tactile extinction	Loss of light touch	Proprioceptive loss	Other disconnection syndromes	Visual disturbance	Corpus callosum lesion	Anatomical localization of the lesion	Alien hand description	Reference
Damage through transcortical operation on of callosal tumor. Also had groping, compulsive tool use, "conflict of intention." No damage in cingulate cortex or supplementary motor area.	No	No	No	Deficits in tactile naming of objects and letters drawn on the left hand, defective cross replication of hand postures	No	Anterior body and splenium	Left parietal cortex and sub cortex	Rt purposeful and purposeless movements	Nishikawa et al. <sup>6</sup>
No frontal signs	Yes	Yes	Yes	No	No	No	Highest portions of the left parietal lobe with minimal frontal extension	Rt levitating hand	Gondim et al. <sup>5</sup>

cited cases also exhibited sensory loss and neglect. However, their postulated explanation might be plausible only for non-dominant hemispheric involvement. In cases like ours, where the lesion involves the dominant hemisphere with no neglect or significant sensory loss, a posterior parietal lesion might not be enough. The appearance of alien hand might then require the constellation of a posterior parietal lesion and interhemispheric disconnection as in our patient. A review of the literature concerning patients with dominant posterior alien hand (Table 1) revealed only two detailed cases. One patient had significant sensory loss, no callosal involvement,<sup>5</sup> while the other patient had no sensory loss but demonstrated other disconnection syndromes suggesting the involvement of the corpus callosum<sup>6</sup> as in our patient. The generation of alien hand might require the incongruity between the visual input, body scheme and motor intention. Since the representation of body scheme is probably prominent in the nondominant posterior parietal lobe, deficient flow of information from this area due to a posterior callosal lesion may contribute to a dominant alien hand phenomenon.

We suggest that the mechanisms underlying some dominant hemispheric alien hands might differ from those of nondominant posterior alien hand with accompanying neglect and sensory loss. In such cases, the possible prerequisite of co-occurrence of a posterior parietal and corpus callosum lesion might explain their scarcity and reported paucity.

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## Continuous Dopaminergic Stimulation: Is it the Answer to the Motor Complications of Levodopa?

We read with great interest the review by Dr. Nutt on Continuous Dopaminergic Stimulation (CDS) in Parkinson's disease (PD).<sup>1</sup> We agree that conventional intermittent levodopa treatment could not mimic the normal pattern of dopaminergic stimulation in nigrostriatal neurons and that alternative strategies to obtain a more physiological response should be sought. Certainly, CDS activation could induce a more physiological activation of dopaminergic receptors and it could be a promising therapeutic option to avoid motor complications deriving from intermittent long-term L-dopa therapy. On these grounds, randomized clinical trials are needed to investigate these issues in parkinsonian patients.

In the case of L-dopa administration, however, at variance with dopamine agonists, CDS strategy may not be fully possible because L-dopa must be converted into dopamine before activating dopaminergic receptors and a continuous modality of L-dopa administration does not necessarily imply a continuous receptor activation. Nevertheless, even if CDS may be unlikely with L-dopa, a more physiological response, dissociating clinical benefit from the presence of dyskinesia, could be reached by exploiting the so called "long-duration" response (LDR) to L-dopa. Indeed this response, resulting from repetitive administrations of the drug and developing over days or weeks after starting treatment,<sup>2</sup> is independent from single intakes of L-dopa which, in turn, determine short-duration responses (SDR) associated with motor fluctuations and dyskinesia.<sup>3,4</sup> On the contrary, the presence of the LDR may ensure a sustained and *tonic* clinical benefit, different from the phasic changes associated with the SDR, whereas the disappearance of the LDR may be relevant for the development of a fluctuating condition.<sup>5</sup> It is unknown whether a tonic release of dopamine may underlay the tonic improvement due to the LDR, but, if this is the case, a continuous administration of L-dopa would not be strictly necessary to obtain this effect. Nevertheless, the mode of administering L-dopa is relevant to obtaining a sustained LDR: for instance, small doses fractionated along the day, as usually done in clinical practice, may fail to elicit and

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