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Letters to the Editor

Cinnarizine-Induced Parkinsonism: Ten Years Later

We read with interest the recent article by Martì-Massò and Poza[1] but we were surprised that our previous paper[2] on the same topic was not quoted by the authors. In fact, the prospective follow-up study[2] we have carried out over a median 5-year period in a small population of patients with cinnarizine (CNZ)- and flunarizine (FNZ)-induced parkinsonism represents, to our knowledge, the first report attempting to characterize possible patterns of clinical course and the long-term prognosis of this syndrome, according to well-defined (although arbitrary) criteria. The same is true for the occurrence and the outcome of coexisting iatrogenic dyskinesias. The overoptimistic results reported by Martì-Massò and Poza[1] showing a complete recovery of parkinsonism in 89% of 74 patients with drug-induced parkinsonism (45 of whom were taking CNZ as the sole drug) are at variance with those of our study[2] and with those of another shorter, prospective follow-up study.[3] Indeed, in our series,[2] a diagnosis of "persistent and not progressive" parkinsonism was still made in 10 of 13 (76.9%) patients at the end of the follow up. This discrepancy may be the result of a less rigorous collection of data which failed to provide evidence of the course of clinical recovery in the patients described by Martì-Massò and Poza,[1] a drawback from which all retrospective studies commonly experience. In fact, it has not been clarified by the authors if their results of completely recovered parkinsonism found at the end of the follow up were obtained indirectly by consultation of medical records or by interviewing patients and/or their family members rather than by personal examination of the affected subjects. In addition, possibly lower cumulative dosages of the offending drug, not reported in their article, could account for the different results of the two studies. Moreover, contrary to published literature,[4] it appears strange enough that completely reversible parkinsonism could be observed in such a high proportion of elderly patients who had been taking neuroleptics in addition to CNZ. Regarding the late development of a progressive syndrome resembling idiopathic parkinsonism, a direct comparison between the results of our study[2] and those of Martì-Massò and Poza[1] is impossible because they did not separate the patients who had been previously exposed to CNZ given as monotherapy from those taking other antidopaminergic drugs concurrently. The lower percentage of patients with persistent dyskinesias at the final assessment of the follow up found in the study of Martì-Massò and Poza,[1] in comparison with the figures reported by us,[2] may also have a bearing on the interpretation of the finding.

In short, we defend our view that the evolution of CNZ–FNZ-induced parkinsonism is not so benign although we recognize that the residual extrapyramidal signs are commonly mild and do not determine significant impairment in motor function.

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Reply

We appreciate Negrotti and Calzetti's comments about our paper.[1] Unfortunately, our manuscript was sent to the editor for the first time before the publication of their article[2] and thus could not be referenced.

We are interested in the long-term prognosis of cinnarizine-induced parkinsonism (CIP), and our experience is more optimistic than Negrotti and Calzetti's.[2] For instance, in our study, 66 of 74 patients with CIP (89%) were completely asymptomatic from 1–16 months after cinnarizine withdrawal. However, a few months later, four of these patients showed parkinsonian symptoms again. In a previous study[3] involving 142 patients with drug-induced parkinsonism (DIP), 82% recovered completely and 16% had later developed idiopathic parkinsonism. Patients taking cinnarizine, flunarizine, flupentixhol, or amiodarone improved better than those taking benzamides, phenothiazines, or butyrophenones. In both studies, the same neurologist has personally examined all the patients during their complete evolution. In Negrotti and Calzetti's series, 10 of 13 (76.9%) patients showed parkinsonian symptoms at the end of follow up, ranging from 2–5 years, and none of their patients completely recovered. This discrepancy may be the result of differences in the composition of both series. Negrotti and Calzetti's series is small and may include severe cases. In contrast, our interest and experience in this matter allowed us to diagnose minimal syndromes with a better prognosis. Our patients

are frequently referred to the neurologist for causes different from parkinsonism. In this way, 24 of our patients had taken cinnarizine for less than 1 year, and all of them recovered completely. The same may be true for dyskinesias.

This leads us to conclude that CIP usually has a good prognosis, especially when an early diagnosis is made.

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Protease Inhibitors Enhance Levodopa Effects in Parkinson's Disease

Long-term treatment with L-dopa can produce abnormal involuntary movements in patients with idiopathic Parkinson's disease (IPD). Peak-dose chorea occurring when plasma L-dopa levels are at their highest have been attributed to changes in the post-synaptic dopaminergic receptors and in the indirect striatopallidal enkephalinergic system.[1] Intermittent and erratic levels of dopamine in the striatum reduce most parkinsonian signs but may provoke dyskinesias, particularly in young-onset and akinetorigid forms of Parkinson's disease treated for more than 1 year.[2] The metabolism of L-dopa and dopamine can be modified by increasing the bioavailability of L-dopa with decarboxylase and catechol-O-methyl transferase (COMT) inhibitors (DCI) or by reducing dopamine degradation with an inhibitor of the monoamine-oxidase B (IMAO-B).[3]

We treated a 66-year-old Afro-Caribbean patient affected by both AIDS (with a 10-year evolution) and IPD simultaneously with L-dopa (plus DOPA decarboxylase inhibitor [DCI]), 2400 mg indinavir per day, 500 mg zidovudine, and 300 mg lamivudine. IPD had been diagnosed 5 years before with the emergence of a unilateral right tremor, akinesia, and rigidity, which worsened progressively and extended to the left side. Treatment with L-dopa plus DCI was well tolerated and induced a 50–60% improvement on the Unified Parkinson's Disease Rating Scale. The patient was free of dyskinesias with 700–750 mg L-dopa per day in the 2 years prior to antiprotease therapy. However, he had unpredictable fluctuations. Computed tomography with and without contrast was normal. After 1 month of treatment with the anti-HIV triple therapy and an unchanged daily dose of L-dopa, the patient developed severe dyskinesias occurring at the peak dose periods, whereas the on-periods lasted the whole day without fluctuations. The dyskinesias consisted of bilateral ballism, most marked in the right arm. The antiviral drugs were stopped and dyskinesias improved within 5 days. The antiviral drugs were later reintroduced separately for a minimum of 2 weeks. Indinavir alone induced the abnormal movements after 3 days of treatment but the two other antiviral drugs did not. No other side effect was observed. Indinavir was definitively stopped and dyskinesias improved within 5 days, whereas the motor status worsened progressively with the reappearance of fluctuations.

Antiproteases are known to inhibit the hepatic metabolism of several drugs by inhibition of cytochrome P450,[4] which catalyzes oxidative reactions produced by MAO or COMT.[5] The latency in appearance and disappearance of this adverse effect, namely, the enhanced effect of L-dopa, could be related to a progressive inhibition of proteases but also to delayed dopaminergic receptor hypersensitivity. The therapeutic effect of protease inhibitors is observed after 10–15 days, whereas cytochrome P450 inhibition occurs after 24–48 hours of treatment.[6] When indinavir and catecholaminergic drugs have to be administered together, this should lead to a reduction in daily requirements of the latter. However, this adverse effect could also theoretically be used to potentiate L-dopa or dopaminergic stimulation as well as (or better than) IMAO-B or ICOMT if confirmed with further studies.

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Decrease in Akinesia Seems to Result From Chronic Electrical Stimulation in the External (GPe) Rather Than Internal (Gpi) Pallidum

I found the article by Krack et al. (Krack P, Pollak P, Limousin P, Hoffman D, Benazzouz A, Benabid AL. Inhibition of levodopa effects by internal pallidal stimulation. *Mov Disord* 1998;13:648–652) interesting for many reasons, one of which is that this article in fact raises one fundamental question: Where is the proper target for relief of akinesia? Is it within the globus pallidus interna (GPi) as most workers (including Krack et al.) suggest or is it in the globus pallidus externa (GPe) as Laitinen continues to insist?

The authors report three patients in whom chronic pallidal stimulation using Medtronic's quadripolar electrode yielded different and contradictory effects depending on which electrode contacts were activated. If stimulation was delivered through the most ventral contact, the patients had less dyskinesias but also less good effect of L-dopa and, subsequently, increased akinesia. If the stimulation was delivered through the most dorsal contact, the effect on akinesia was better but at the cost of slightly persisting dyskinesias.

Concerning the precise anatomic location of the four electrode contacts within the pallidum of the three reported patients, the authors refer to another paper in which they described in detail "the opposite motor effects of pallidal stimulation in Parkinson's disease."[1] From this study (which in abstract form was rewarded a prize for best poster presentation at the XII International Symposium on Parkinson's Disease in London in March 1997[2]) it appears that the most ventral contact of the quadripolar electrode was, in the great majority of cases, not even in the Gpi but just below the Gpi. On the other hand, the most dorsal electrode in the majority of cases is in the Gpe or at best in the dorsal Gpi close to the Gpe. It should be remembered that the most dorsal contact of the used electrode lies 8 mm above the most ventral one, and more than 10 mm separate the areas of the brain receiving stimulation from the most dorsal and most ventral contacts, respectively.

If we assume, together with the authors, that high-frequency electrical stimulation inactivates or blocks a neural structure, that is, electrical stimulation mimics the effects of ablation, then it stands to reason that the best effects on akinesia were actually stemming from electrical inactivation of the Gpe and not from stimulation of the Gpi or the area just below the Gpi. Inversely, electrical stimulation of the most medial Gpi or the area just ventral to it resulted in inhibition of L-dopa effect and an increase in akinesia. This is in fact exactly what Laitinen has been claiming in contrast to the opinion of the overwhelming majority of the neurologic and neurosurgical community involved in research and surgery on the pallidum.[3] Laitinen has insisted on avoiding lesioning the medial Gpi but rather "releasing" the overactive Gpi by placing the pallidotomy lesions laterally, in the Gpe, and he continues to call his pallidotomies "ventroposterolateral"[4] in opposition to those who insist that the pallidotomy should be ventroposteromedial, that is, in the Gpi.

Lang and Lozano, who are strong advocates of the internal pallidum as a target, have made similar observations as Krack et al.[5] The Heidelberg group, also reporting negative effects of GPi stimulation on akinesia, questions this method as "a real alternative to pallidotomy."[6] On the other hand, several workers such as Koller et al.,[7] Siegfried et al.,[8] and Gross et al.[9] did not mention such contradictory stimulation effects in the pallidum. In fact, the observations made by Krack et al., when they electrically blocked the outflow from the most ventral and medial GPi by stimulating the most ventral electrode contacts, are similar to what is known of thalamotomy effects, that is, a decrease in rigidity and dyskinesias but an increase in akinesia. This is another reason to avoid placing the lesion (or the electrode tip for that matter) in the most medial and most ventral GPi.

In my modest, and therefore yet unpublished, experience of chronic pallidal stimulation, I found that if the most ventral contact happens to lie in the most ventral Gpi or below, the akinesia is indeed not relieved and in some cases the freezing of the gait even becomes worse. Therefore, I do agree with the authors that electrical stimulation through more dorsal and especially more lateral contacts (given an anteroposterior and slightly lateromedial electrode trajectory) yields the best effects for akinesia and rigidity and, to a great extent, for dyskinesias.

I hope Krack et al. will draw the logical conclusions from their excellent and meticulous work by abandoning the confusing and seemingly erroneous term "Gpi" stimulation, because what actually helped to decrease the cardinal parkinsonian symptom of their patients was, in fact, a Gpe stimulation.

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Reply

We owe the renaissance of pallidotomy to the work of Drs. Laitinen, Bergenheim, and Hariz,[1] and we feel honored by the kind comments of Dr. Hariz on our work describing experimental high-frequency stimulation (HFS) of the pallidal area and chronic therapeutic HFS of the GPi.[2–5] The same results have been found independently and simultaneously by Bejjani and coworkers.[6,7]

With all due respect and friendship, however, we do not agree with the conclusion of Dr. Hariz that the beneficial effects of pallidal HFS result from an inhibition of the external (GPe) rather than the internal (GPi) pallidum because this conclusion is based on several premises that we do not share:

1. *HFS does not block neural structures, whatever the target.*

Although HFS of three different targets for PD surgery, that is, the ventral intermediate nucleus of the thalamus (Vim), the subthalamic nucleus (STN), and the GPi, is suggested to functionally inhibit these targets as it mimics the effects of a lesion in all three targets, one cannot conclude that HFS is the same as lesioning anywhere in the brain. The frequency of stimulation is a critical parameter, because therapeutic effects are not observed below 50 Hz.[8] However, HFS does not inhibit every part of the brain. HFS of the pyramidal tract induces muscular contraction. Thus, some structures, mainly fiber, can be activated and not inhibited when they are electrically stimulated, even at a high rate.

2. *Acute experimental HFS cannot be equaled with chronic therapeutic HFS.*

It is important to bear in mind that the different effects obtained stimulating the different contacts of the quadripolar electrodes (which are not all within the GPi) were obtained in an *experimental* setting using *acute* stimulation and up to *high voltage*, therefore possibly decreasing the spatial selectivity. The effects of *therapeutic chronic* stimulation of the GPi using *low voltage* were close to the effects reported for internal pallidal lesions. As Dr. Hariz correctly points out, the dorsal contacts were partly located within the GPe. Thus, part or most of the effects of acute high-voltage stimulation of the dorsal contacts would possibly be explained by influencing the GPe or fibers passing in this area. However, the effects of acute stimulation of the dorsal contacts have a completely different time course than those of chronic stimulation using electrodes located within the GPi. Immediately after surgery, the acute stimulation of the dorsal contacts can lead, with a latency of seconds up to several minutes, to a sudden improvement of akinesia which can be dramatic, even bilateral, and resemble acute "turning on" with levodopa, including the induction of dyskinesias which also resemble those induced with levodopa. Unfortunately, however, this acute effect does not last. It may last from minutes to a few days but will finally wear off as we have observed in several patients, and in the long run parkinsonism may worsen. The effects of GPi-HFS that we reported for acute experimental stimulation 3–6 months after surgery were mild and never exceeded 1 point on the 5-point ranking scale of the respective akinesia item of the Unified Parkinson's Disease Rating Scale[4]; they were most often found on the dorsal contacts 2 or 3 in the dorsal GPi or above. The effects on parkinsonism related to chronic stimulation of electrodes lying within the GPi, on the contrary, gradually build up. On chronic stimulation, using the contacts lying either within the GPi or sometimes below but never above the GPi,[4] the patients were improved as reported in our case reports[5] and in the results of the entire group of patients.[4] Improvement included gait and hand-tapping speed in the off-drug period.

3. *HFS does not only influence nuclei, but may also influence fibers.*

Although there is a functional somatotopy within the GPi,[9–11] we have favored a modulation of the main outflow structures of the GPi as an explanation for the opposite side effects of acute experimental stimulation of the most ventral and most dorsal contacts.[4] Both the ascending efferent connections of the GPi to the thalamus[12] and the descending pallidotegmental fibers[13] are segregated. If the output channels subserve different signs, it is more likely that these signs are separately modulated by HFS of the fiber systems rather than within the target where they are tightly intermingled.

As already pointed out, stimulation of the pyramidal tract induces muscular contractions without habituation. On the other hand, visual flashes induced by stimulating electrodes, which are close to the optical tract, rapidly disappear. Dysesthesias related to stimulation of sensory fibers may or may not disappear with chronic stimulation. Within the thalamus, stimulation of the Vim induces transient paresthesias supposed to be related to diffusion to the ventroposterolateral (VPL) sensory thalamus,[14] the stimulation of which may induce permanent paresthesias. Lesions too do not only pertain to effects on the neurons of a defined structure or to a single tract. Meyers, who introduced basal ganglia surgery, was aware of this. When he proposed what later was called ansotomy, he drew a diagram showing a section not only of the ansa lenticularis, but also of the fasciculus lenticularis and of the fibers between the GPi and the brain stem (see reference 15, Fig. 255 on p. 651) which today we would refer to as pallidonigral, pallidotegmental, and STN-GPi fibers based on our better understanding of anatomy and physiology.[16]

Recent work has questioned the sensorimotor role of the ansa lenticularis.[17] If this preliminary work turns out to be correct, it seems unlikely that the levodopa-inhibiting effects related to HFS of the ventral contacts lying below the GPi are mediated through the ansa lenticularis. The pallidotegmental fibers then become good candidates to explain the worsening of akinesia, the inhibition of levodopa, and the fact that these effects can be bilateral. Lesioning the pedunculopontine nucleus (PPN) in the monkey unilaterally leads to marked akinesia, which can be bilateral, with the monkeys recovering within a few days.[18,19] A bilateral lesion leads to long-standing generalized akinesia.[19] This akinesia does not respond to levodopa (Aziz, personal communication). The PPN receives GABAergic fibers from the GPi.[13] An activation of these fibers would result in an inactivation of the PPN, which could explain a bilateral worsening of akinesia resistant to levodopa as observed in acute experimental, unilateral HFS of the ventral contacts lying below the GPi (see reference 5, video segment 4). We have also observed a marked bilateral motor inhibition or akinesia together with tremor arrest and suppression of rigidity related to acute experimental HFS of an electrode lying just 4.5 mm below an electrode located in the STN, the stimulation of which induced improvement of contralateral akinesia, rigidity, and tremor. The

electrode inducing the akinesia was located in the area of the substantia nigra (SN) or slightly more lateral in the cerebral peduncle according to the Talairach atlas.[20] This effect seems to be identical, although more marked, than that described for HFS of the ventral contacts below the GPi. This effect too could be tentatively explained by an activation of GABAergic fibers from the substantia nigra pars reticularis (SNr) to the PPN.[16] However, other fiber systems must also be considered such as the corticoreticular fibers[21,22] within the internal capsule (for GPi) and the cerebral peduncle (for SNr).

The effect of acute experimental stimulation of contacts lying in the dorsal GPi or the GPe is reminiscent of the effect of levodopa and of the effect of STN-HFS. Activation of the glutamatergic STN-GPe fibers by HFS of the dorsal contacts could lead to an overactivation of the GPe and thus to an inhibition of the STN through the GABAergic GPe-STN fibers. A direct activation of the GABAergic GPe-STN fibers could also account for the levodopa-like effect observed with acute experimental HFS of the dorsal contacts.

4. *An inhibition of the GPe does not improve akinesia or levodopa-induced dyskinesias.*

According to the classic scheme of the basal ganglia organization,[23] levodopa-induced dyskinesia is related to overactivity of the GPe, and ablation of the GPe would be predicted to worsen parkinsonism as a result of disinhibition of the STN. Indeed, excitotoxic lesions of the GPe (sparing fibers) do not relieve levodopa-induced dyskinesia in MPTP parkinsonian monkeys and can worsen the akinesia for a few days in case of a unilateral lesion.[24] Moreover, injection of the GABA antagonist bicuculline into the GPe of intact monkeys leads to dyskinesias[25] associated with GPe neuronal hyperactivity.[26]

To diminish the risk of optic tract lesions, Dr. Laitinen gradually moved the target in a lateral direction, and he found a better improvement of parkinsonism. He called this approach a ventroposterolateral pallidotomy,[27] insisting that in most patients the lesions were lateral to the GPi.[28] The verification of the lesions was based on stereotactic computerized tomography and magnetic resonance imaging.[29] These postoperative studies indicate that his target was lying between the medial and the lateral pallidum, close to the putamen. Laitinen, Bergenheim, and Hariz have proposed that the ventroposterolateral pallidotomy, encroaching on the GPe, may interrupt direct striatopallidal and indirect striatopallido(GPe)-subthalamic pathways and thus prevent GPi cellular hyperactivity from developing.[28,30,31] The authors are correct to consider fiber tracts in addition to neuronal cell bodies within a target. We must not forget that the globus pallidus is called pale (pallidus meaning pale in Latin) because of the numerous fibers crossing this nucleus. However, there is overwhelming evidence now that lesions placed within the GPi rather than within the GPe improve akinesia and LID.[11,32–35] The exact localization using microrecording and stimulation to precisely localize the sensorimotor region of the GPi as well as the size of the lesion within the GPi may be critical to induce optimal benefit.[10,11,36]

Conclusions

A monopolar stimulation of a single contact was used for chronic therapeutic pallidal HFS in all our patients. In all the patients, the contacts lying within the GPi or even below, never the most dorsal contacts lying within the GPe, were used for chronic stimulation. The average voltage was 3.5 ± 0.2 V, and the impedance of the electrodes generally was approximately 1000 Ω. Thus, the current used was approximately 3.5 mA. The average pulse width was 97 ± 28 μs. Using these parameters, the diffusion of the current was restricted to a few millimeters as shown by the different effects and side effects obtained using the different contacts of the quadripolar electrodes. Therefore, we think the beneficial effects of chronic pallidal HFS on all the parkinsonian signs and on dyskinesias are related to an electrode that is well placed within the GPi. Our findings of a differential effect of HFS on parkinsonian signs, depending on the exact location of the electrode within the GPi, have been corroborated meanwhile by a differential effect on rigidity and dyskinesia, akinesia, and tremor depending on the exact localization of a pallidal lesion within the GPi.[10,11] The effects of the acute experimental HFS of the dorsal and ventral electrodes using high voltage is more difficult to interpret because diffusion of the electrical current may influence different structures. It is important, however, to know the effects and side effects of experimental HFS of neighboring structures when programming the stimulators for GPi stimulation. Not only inactivation of the target, but also activation of fiber tracts may account for some of the reported side effects of acute experimental HFS. The GPe may be influenced by acute experimental HFS but the effects of chronic HFS of the pallidum cannot be explained by inhibition or activation of the GPe. If experimental HFS above and below the pallidum reproduces the effects of chronic therapeutic HFS of the GPi and of GPi lesions, that is, improvement in rigidity, akinesia, tremor, and levodopa-induced dyskinesias, then it seems likely that experimental HFS alters the input or output fiber activity of the GPi. Two of the symptoms induced by acute experimental HFS are not reported as being effects of therapeutic lesions restricted to the GPi and therefore need a separate discussion.

1. *HFS of the dorsal GPi or above the GPi can induce dyskinesias together with a levodopa-like effect on parkinsonism.* These stimulation-induced dyskinesias have the same semiology as the levodopa-induced dyskinesias in an individual patient.[4] Dyskinesias, generally lasting less than 60 seconds, have also been reported to occur during pallidal surgery and to be predictive for a good outcome.[37] Chronic HFS and pallidotomy do not induce long-lasting dyskinesias, and the improvement of LID is one of the most consistent findings of pallidotomy and pallidal HFS. The effect of HFS of the GPi on dyskinesias is direct and immediate[5] as opposed to the effect of STN HFS in which on-period dyskinesias are mainly reduced indirectly by a reduction of levodopa.[38–41] Although the best therapeutic effects are found with chronic HFS of the electrode contact in the STN that induces the most severe dyskinesias, this is not the case for pallidal stimulation. Thus, it is possible that the induction of dyskinesias stimulating the upper contacts is not related to the target itself, but rather to diffusion into neighboring structures, either the GPe or bypassing fibers.

2. *HFS of the ventral GPi or below the GPi can inhibit the effect of levodopa not only on dyskinesias, but also on akinesia.* Akinesia can be worsened beyond the worst-off akinesia.[5] Chronic HFS of the GPi[4,5,42–46] and pallidotomy[30,32,33,47] improve akinesia. The worsening of akinesia could be related to selective modulation of pallidal outflow fibers. Activation of the pallidotegmental fibers could explain not only the bilateral

worsening of akinesia, but also the bilateral inhibition of the levodopa effect on akinesia.

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