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Letters to the Editor

Antiparkinsonian Treatment in Pregnancy

We read with interest the article by Shulman and colleagues in a 2000 issue of *Movement* Disorders.[1] In that article, one case of pregnancy in a patient with Parkinson's disease (PD) on levodopa therapy was reported. After prospective and quantitative neurological examination of the patient, the authors concluded that pregnancy exacerbates PD and could have a long-term negative impact on the course of the illness.

A few cases of pregnancy in parkinsonian women have been described; all of these patients were treated with levodopa but none demonstrated major drug teratogenity.[1–4] Moreover, dopamine agonist treatment during pregnancy of PD patients has been reported by Benito-Leon and associates[3] as a bromocriptine monotherapy; another patient described by Hagell and coworkers[2] discontinued bromocriptine after 2 months of pregnancy. In neither case did bromocriptine treatment result in any teratogenity. Pergolide administration in parkinsonian women during pregnancy has not been reported previously. We describe a woman with PD treated with combined pergolide and levodopa therapy during pregnancy.

A 36-year-old woman developed PD with progressive motor slowness in the left limbs at age 32 years in 1996. At the first examination, she presented a slight rigidity and bradykinesia to the left arm and leg and a mild hypomimia. There was no evidence of resting tremor. Hoehn and Yahr rating was 2. Evaluation for other causes of parkinsonism revealed no significant abnormalities. Family history for PD was not reported. Treatment with pergolide up to a dose of 1 mg three times daily resulted in partial improvement, and after 6 months levodopa was added at a dose of 200 mg per day, resulting in optimal control of her symptoms. After 2 years the patient complained of a predictable wearing-off period in the afternoon, demonstrated as slight bradykinesia, mild rigidity in lower limbs, and gait disturbances such as short steps and shuffling, mainly in her left leg.

When the patient became pregnant at age 35 years, the dosage of pergolide and levodopa was continued throughout the pregnancy. During the pregnancy, all wearing-off phenomena disappeared and she had optimal control of motor symptoms throughout the day. She gave birth to a normal-term infant in July 2000 with Apgar scores of 9, by cesarean section, because of a podalic presentation. The child shows no evidence of congenital malformation and remains healthy at this time, 13 months of age, with normal development. During the puerperal period the end-of-dose wearing-off symptom reappeared and reached the same level as before pregnancy.

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To our knowledge, this is the first description of combined pergolide and levodopa treatment during pregnancy in a woman with PD. Except for one case of osteomalacia and another of spontaneous abortion, for which the cause is not well established, no major complications of pregnancy, nor any adverse effects on the fetus that could primarily be related to levodopa plus carbidopa or benserazide have been reported in the literature.[1–7] Studies of carbidopa–levodopa in laboratory animals demonstrated some increase in skeletal malformation but only with high doses, greater than 500 mg/kg/day.[6]

Among antiparkinsonian treatment, amantadine has shown teratogenicity in a case of cardiovascular maldevelopment, associated with maternal exposure, during the first trimester of pregnancy.[8] The use of amantadine as an antiviral treatment or prophylaxis has been discouraged in pregnant women.[9]

Hagell and associates[2] held that treatment with the dopamine agonists bromocriptine and lisuride was safe during pregnancy. Furthermore, in premarketing studies of pergolide for endocrine disorders, two major and three minor congenital abnormalities were described among 38 pregnancies, but a causal relationship has not been established. Pergolide has not shown evidence of harm to fetuses in mice or rabbits in animal studies.[10,11] There is no information regarding pregnancy and pramipexole or ropinirole therapy. Although levodopa and some dopamine agonist treatments are reported not to cause pregnancy complication, the effects of pregnancy on the symptoms of PD seem to be controversial. In the review by Hagell and colleagues,[2] it was reported that in 46% of pregnancies PD symptoms worsened or new symptoms occurred during or shortly after pregnancy. Few reports have observed that a patient's symptomatology remained stable or without any complication throughout pregnancy.[2,3,5] The patient described by Shulman and coworkers[1] experienced marked worsening of motor symptoms and a need for progressively higher levodopa dosages throughout the pregnancy, reaching a peak dose in the postpartum period. The author's impression was that pregnancy may have worsened PD symptoms, both during the last period of pregnancy and in the postpartum period, suggesting a role for estrogens on the dopaminergic system. When analyzing this case, the worsening of parkinsonian symptoms in this particular patient occurred in the last period of the pregnancy and in the postpartum period, at a time when estrogen levels are low. The high estrogen levels during pregnancy could play a beneficial role, improving parkinsonian symptoms, considering the dopaminergic-sparing properties of this hormone resulting from interaction with catechol-O-methyltransferase enzyme.[12,13] Furthermore, a recent study described a beneficial effect in PD from estrogen replacement therapy.[14] Other authors have suggested that the changes in parkinsonian symptoms of PD women treated with antiparkinsonian drugs during pregnancy could be the result of a natural disease progression,[2] or that pregnancy induced pharmacokinetic modification.[6] Moreover, as suggested by Shulman and colleagues,[1] physical and psychosocial stressors could play an additional role, ex-

plaining the variability of parkinsonian symptomatology reported during pregnancy.

In our patient the role of estrogen on the dopaminergic system, and psychosocial factors such as the desire to become pregnant, could explain the optimal control of motor symptoms, which worsened slightly in the postpartum period. Our experience seems to confirm the need of continuing antiparkinsonian treatment during pregnancy to avoid deterioration of symptoms. We also describe the apparent safety of pergolide therapy during pregnancy in parkinsonian women, which has not been demonstrated previously. In addition, combination therapy with pergolide and levodopa was useful for optimal control of PD symptoms during pregnancy, as it resulted in disappearance of motor fluctuations.

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Deep Brain Stimulation in Huntington's Disease

In his excellent review, Joel[1] suggests deep brain stimulation (DBS) of the globus pallidus externus (GPe) in Huntington disease (HD). This, in fact, is a very challenging hypothesis, as the majority of the new neurosurgical techniques for medically intractable movement disorders is performed in patients with hypokinetic movement disorders, especially Parkinson's disease (PD). Moreover, no enduring therapeutic benefit has been reported so far in HD; only transient improvement of choreatic symptoms has been seen with neuroleptic medication.[2] However, we suggest targeting the substantia nigra pars compacta (SNc)[9] instead of the GPe for the following reasons. We observed a total relief of chorea in a patient with clinically, radiologically, and genetically confirmed HD after he had suffered marked choreatic symptoms for years.[3] Careful analysis of cranial magnetic resonance imaging (MRI)[4] disclosed a marked bilateral degeneration of the substantia nigra in this case, which was not present at the time of chorea. In fact, choreic movements have never been encountered in combination with nigral degeneration.[5] Moreover, nigral atrophy secondary to striatal degeneration fails to produce parkinsonian symptoms,[6] whereas parkinsonism disappeared in patients with PD after ischemic striatal lesions[7] (striatal atrophy is the morphological hallmark in HD). It has been known for decades that dopaminergic antagonists (i.e., phenothiazines or butyrophenones) are temporarily successful in treating choreiform dyskinesias,[2] whereas dopamine agonists can induce choreatic movements[8]; both facts have caused interpretative difficulties until now.

Interestingly, in Pick's disease, a neurodegenerative disorder without choreatic movements, severe striatal atrophy similar to HD occurs, but is accompanied by neuronal loss in the SNc.[9] In the rat model of HD, striatal dopaminergic afferents not only sustain the toxic insult of quinolinic or kainic acid, but react by even further increasing their activity.[10–13] This can be explained by degeneration of γ-aminobutyric acid (GABA)ergic neurons with subsequent disinhibition of dopaminergic neurons, suggesting reciprocal inhibition of SNc and the striatum.[14,15] Striatal degeneration may so induce dopaminergic hyperactivity, thus creating chorea.

Lesions of the subthalamic nucleus (STN) may result in transient hyperkinesia in otherwise healthy primates.[16,17] However, STN lesioning fails to result in hyperkinesia in primates with artificial SNc lesions, but reverses experimental parkinsonism.[18] Moreover, therapeutic lesions of the STN have been carried out successfully in PD patients,[19] indicating that dopamine deficiency causes disinhibition of the STN (which, on the other hand, is overactive in chorea).

Blockade of the striatal GABAergic input to the GPe causes chorea in primates.[20] This finding favors the suggestions of Joel.[1] However, electrophysiological studies in rats[21,22] have shown that GPe lesions only produce a 20% increase in the

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firing rate of STN neurons, whereas lesions of the nigral pathways results in a 100% increase in such firing, indicating the importance of the dopaminergic system.

Dopamine, in fact, exerts a neurotoxic effect in vitro.[23] Apoptosis appears to be the underlining mechanism, which is further enhanced when mitochondrial function is concomitantly compromised,[24] as observed in HD patients,[25] thereby creating a scenario for an increasing cycle of neuronal loss in the striatum which could be stopped or slowed down by lesioning the SNc.

Finally, in 1965, Zapletal[26] reported stereotactic nigrotomies in four cases of unilateral choreoathetosis that were not successful. However, as he reported in the same publication, for the therapeutically successful "nigrotomies" of six PD patients, the author probably targeted the substantia nigra pars reticulata (SNr), if he reached the substantia nigra at all (his procedures relied on macroscopic surgical vision for the identification of the target area). Lesioning the globus pallidus internus (GPi) in PD is known to relieve Parkinsonian symptoms.[27–30] As the SNr, like the GPi, is overactive in PD,[31] targeting the SNr apparently has the same ameliorative effect as lesioning the GPi.

We suggest for all these reasons that the striatal degeneration underlying the choreatic movement disorder in HD can be counteracted more powerfully by lesioning the SNc.

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Deep Brain Stimulation in Huntington's Disease: Globus Pallidus Externus or Substantia Nigra Pars Compacta. Reply

In response to our suggestion that lesion to the external segment of the globus pallidus (GPe) could ameliorate some of the symptoms of Huntington's disease (HD),[1,2] Bonelli and Gruber[3] submit that a better strategy would be to target the substantia nigra pars compacta.

The data presented by Bonelli and Gruber are of great interest and relevance for the understanding of the pathological mechanisms underlying HD symptomatology and for developing new therapeutic methods for this debilitating disease. Importantly, their letter may stimulate a timely discussion on the possibility of using neurosurgical techniques for the treatment of HD.

Our proposition that lesion to GPe may alleviate some HD symptoms was based on a model of the functional anatomy of basal ganglia–thalamocortical circuitry and the known pathology of HD, and corroborated with supportive evidence from a rat model of this disease.[4] Bonelli and Gruber derive their proposal from a dramatic case of an HD patient who had a total relief of chorea following bilateral degeneration of the substantia nigra, and from several other lines of evidence suggesting that striatal damage leads to chorea only when the dopaminergic (DA) input to the striatum is intact.

The case presented by Bonelli and Gruber as well as the other examples of combined striatal and nigral degeneration that do not lead to chorea (see Bonelli and Gruber[3] for references) can be accommodated by current models of basal ganglia–thalamocortical circuitry and by our model-based account of HD symptomatology.[1,2]

As pointed out by Bonelli and Gruber, it has been long known that hyperkinetic movements are exacerbated by DA agonists and suppressed by D2 receptor antagonists. Albin, Young, and Pennry[5] pioneered the suggestion that, because D2 antagonists potentiate the activity of striatal neurons projecting to the GPe, their administration in HD "would result in the stimulation of the remaining striatal-GPe neurons and partially overcome the deficit created by degeneration of this subpopulation of projection neurons" (p. 370).

Subsequent models of basal ganglia–thalamocortical circuitry have incorporated findings of the differential expression of D1 and D2 receptors on neurons of the direct and indirect pathways, respectively,[6,7] as well as findings that activation of D2 receptors inhibits striatal neurons,[8–12] whereas activation of D1 receptors enhances the response to excitatory input of striatal neurons in the *up* state but reduces the response of neurons in the *down* state,[10,13–17] and consequently suggested that DA input to the striatum acts to facilitate wanted movement via the direct pathway and to disrupt the suppression of unwanted movement via the indirect pathway.[18–20]

It follows from the latter that if the pathological mechanism of Huntington's chorea is underactivity of indirect pathways, then an intact DA input to the striatum would be crucial for the expression of chorea in HD, as an inability to suppress inappropriate movements would be manifested only if movements are initiated by the direct pathway. Depletion of striatal DA would both reduce movement initiation and increase the ability to suppress inappropriate movements, and would therefore be expected to alleviate chorea, as has indeed been suggested by Bonelli and Gruber.

Regretfully, Bonelli and Gruber relate only to the appearance and disappearance of chorea in their patient. HD patients usually suffer also from cognitive and emotional disturbances. According to our previous account of HD symptomatology,[1,2] these symptoms are also the result of disrupted basal ganglia circuitry. Specifically, we have suggested that the motor and emotional symptoms of early HD result from the degeneration of several indirect pathways, whereas the cognitive symptoms result from the degeneration of direct and indirect pathways. It can therefore be speculated that inactivation of the substantia nigra pars compacta (SNC) may alleviate symptoms resulting from underactivity of indirect pathways, that is, chorea, as suggested by Bonelli and Gruber, as well as affective and some of the cognitive (i.e., cognitive disinhibition) symptoms characteristic of early HD. However, SNC inactivation is also expected to result in the worsening of symptoms resulting from underactivity of the direct pathway, namely, impaired "executive" functions (such as planning, selecting, initiating, and sequencing motor programs, mental flexibility, and set shifting). The potential advantage of GPe inactivation is that it is expected to alleviate symptoms resulting from degeneration of indirect pathways while having no effect on symptoms resulting from degeneration of direct pathways. In other words, GPe inactivation is expected to have the beneficial consequences of SNC inactivation without its deleterious effects.

Finally, Bonelli and Gruber's suggestion that inactivation of the SNC may slow the progressive striatal degeneration in HD is very appealing and requires investigation. We have previously suggested that lesion to the GPe may slow down the progressive striatal degeneration in HD, because the latter has been suggested to depend on increased corticostriatal excitatory input,[21–23] which would be expected to be normalized by the GPe lesion. Although our initial findings in the quinolinic acid rat model of HD using electrolytic lesion of the globus pallidus (the rat analog of the primate GPe) supported this hypothesis,[4] later experiments using an excitotoxic pallidal lesion did not demonstrate an effect on the extent of striatal damage (unpublished observations). This lack of effect, however, may be due to the fact that, in contrast to a previous report,[24] we have found no evidence that the striatal lesion progresses following an intrastriatal injection of quinolinic acid. The lack of progressive degeneration in the rat model prevents the assessment of the effects of pallidal lesion on such degeneration.

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Erratum

Scarmeas N, Eidelberg D, Frucht SJ. Oculogyric-like crises in a 92-year-old woman with vascular parkinsonism. Mov Disord 2001;16:353–355.

In the above Clinical/Scientific Note, the leading author's name was incorrectly listed as Nicholas Scarmato. The correct spelling of the name is Nicholas Scarmeas.