mality" in the CSF of this patient. But it is unclear whether an isoelectric focusing was performed in this case.

POT is thought to be generated by a unique supraspinal tremor generator due to highly coherent tremor activities in cranial, arm, and leg muscles on both sides.[5,6] The presence of such a tremor generator points to a functional or even structural lesion within the central nervous system (CNS). Different possible etiologies for such a lesion can be discussed: this lesion can be, for example, of inflammatory, ischemic, or primarily neurodegenerative origin. A solely inflammatory etiology of POT is rather unlikely considering our normal CSF findings and the normal cerebral imaging studies in POT patients.[3,4,7] The normal cerebral imaging studies and the chronic progressive course contradict an ischemic etiology of POT. The creeping onset and the chronic progressive and oligosymptomatic course most likely suggest a primarily neurodegenerative etiology of POT. This degeneration seems to be sporadic and not hereditary since there is no evidence of any heritability of POT.[3]

In summary, inflammatory CNS changes, as suggested by the case report of Trip and Wroe,[1] seem to play a less important etiological role in POT. The POT is most likely a sporadic, primarily neurodegenerative disease. More reports about CSF findings in POT patients are necessary to corroborate this assumption.

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Trimetazidine: A New Cause for Drug-Induced Parkinsonism?

Trimetazidine is widely used in angina pectoris and in ischemia of neurosensorial tissues as in Ménière's disease.[1] Recently, Marti-Masso reported 8 cases of parkinsonism induced by this drug.[2] We report here a new case of extrapyramidal syndrome observed with this drug.

Case Report

A 91-year-old woman presented to us in January 2002 with malaises occurring several times a week with falls. She suffered from these symptoms for several months and was treated for vertigo with oral trimetazidine (35 mg b.i.d.) for 9 months plus oral nicardipine (50 mg b.i.d.) for arterial hypertension. The clinical symptoms usually disappeared in the lying position. Examination revealed first orthostatic hypotension (180/90 mm Hg in lying and 140/80 mm Hg in standing position) and, second, facial hypomimia, bilateral bradykinesia, and cogwheel rigidity with walking "à petits pas," plus postural instability. There was no resting tremor. The patient also suffered from urinary incontinence and her Mini-Mental State examination score was 22. No other neurological or general abnormality was found. Computed tomography scan was normal for her age, without any sign of normal pressure hydrocephalus. Trimetazidine was stopped, and 2 months later (at the following visit), all the extrapyramidal symptoms had disappeared. Orthostatic hypotension without any increase of heart rate during orthostatism still persisted. Clinical symptoms remained stable for 3 years without any reoccurring of extrapyramidal symptoms (last follow-up in December 2004).

Discussion

Drug-induced parkinsonism is the most important cause of secondary parkinsonism.[3] The drugs most frequently involved include dopamine antagonists (i.e., true neuroleptics used as antipsychotic but also "hidden" neuroleptics prescribed as antinausea or anti-vomiting drugs such as metoclopramide or other benzamide derivatives), dopamine-depleting drugs (reserpine, tetrabenazine), or alpha-methyl-dopa.[3] Moreover, since the 1980s, several authors have described cases of parkinsonism related to the use of two calcium channel blockers: flunarizine and cinnarizine.[3] In fact, the extrapyramidal symptoms induced by these drugs are explained by their main pharmacological properties because flunarizine and cinnarizine are also potent antagonists of the central D2 dopamine receptor.[3]

The present report suggests a role for trimetazidine in occurrence of such an adverse drug reaction (ADR). Using the criteria of the French network of pharmacovigilance centers,[4] the imputability score (i.e., the causality assessment) was found

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as "plausible" with a reasonable temporal relationship to drug intake and no other case of parkinsonism. Moreover, 2 years after trimetazidine withdrawal, none extrapyramidal symptomatology has reoccurred.

Marti-Masso[2] recently described 8 cases of parkinsonian symptoms related to trimetazidine. The clinical symptoms included typical extrapyramidal rigidity with bradykinesia. Tremor was found in only 4 cases. Patients were between 72 and 94 years old and had received the drug for 6 to 12 months (except 9 years for 1 case). Parkinsonian symptoms always disappeared after trimetazidine withdrawal. More recently, the regional pharmacovigilance center from the Basque country reported 3 other cases in Spain and found 3 others in the World Health Organization database in Uppsala, Sweden.[5]

The clinical characteristics of this serious and unexpected ADR seem to be similar to those observed with flunarizine or cinnarizine. Bradykinesia and rigidity are common, whereas tremor only occurred in some patients.

The mechanism explaining such an ADR remains unknown. However, due to the presence of a piperazinic nucleus (as observed in flunarizine or cinnarizine formula), one could suggest that a blockade of central D2 dopamine receptors could be involved.

Finally, the present case report as well as the review of the literature clearly suggest that trimetazidine could induce parkinsonian symptoms in some aged patients. These observations also underline the need of a reassessment of the benefit/ risk ratio of trimetazidine in the light of future studies investigating the true incidence of such an ADR.

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Botulinum Toxin Type A Therapy During Pregnancy

We read with great interest the recent article by Newman and colleagues[1] on botulinum toxin type A therapy during pregnancy. We, too, have had experience with two patients who received botulinum toxin type A injections during pregnancy.

The first patient was a 38-year-old woman receiving an average dose of 150 units of Botox for 3 years for a total of seven injections for cervical dystonia. She elected not to employ contraception despite recommendation because of a previous diagnosis of infertility. Unaware that she was 2 weeks pregnant; she received 200 units of Botox. Her only other medication at that time was alprazolam. She had a healthy term baby delivered by cesarean section.

The second patient was a 39-year-old woman with cervical dystonia receiving an average dose of 315 units of Botox for 3 years for a total of 14 injections. Concomitant pharmacotherapy included benztropine, clonazepam, and fluoxetine. She was advised of the recommendation of contraception before each injection. Unaware that she was 4 weeks gestation, she received 500 units of Botox. Two weeks later after informing us of her pregnancy, she was referred to a high-risk pregnancy obstetrician and to the genetic department for counseling. All medications were discontinued. An ultrasound carried out later detected twin gestation of 10 weeks with no fetal heartbeat. She had one miscarriage before this pregnancy.

The first case along with others[1,2] did not have any obvious adverse effects on the fetus, whereas the second case ended in a miscarriage. It is difficult to determine if the Botox exposure in the second case was a causative factor of the fetal demise given the other risk factors including patient's age, medications, twin gestations, and prior history of miscarriage. However, she had received a relatively larger dose during the last injection. The case by Newman and colleagues[1] is different from ours given that the patient was injected throughout her pregnancies, whereas our 2 patients were injected only once in the first trimester. Although much more investigation is needed to determine the safety of botulinum toxin type A use during pregnancy, it is important to know that botulinum toxin type A can be given safely, as demonstrated by Newman and associates in this case.[1,2] Once it was known that our first patient was pregnant, she was not injected any further during the pregnancy. She did suffer from a severe exacerbation of her cervical dystonia until she was restarted on Botox injection after the

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