The interest of this paper lies not so much with the proven benefits of methylprednisolone therapy in NMS in Parkinson's disease, as in the high incidence of NMS in the Japanese patients treated in this unit. I would value the author's further comments.

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Authors' reply

We greatly appreciate Dr Clark's comments about our work on the efficacy of methylprednisolone pulse therapy in neuroleptic malignant syndrome (NMS) in Parkinson's disease.[1] We agree with him that 40 cases of this syndrome identified from a single institute over three years in patients with Parkinson's disease is a large number. The study institution—the Futase Social Insurance Hospital—is a specialised centre for neurological diseases, particularly among elderly patients, and we have treated several hundred patients with Parkinson's disease. Furthermore, half the NMS patients were transferred from other non-specialised hospitals and private offices in the area. The large number of patients and inappropriate treatment in some patients resulted in an accumulation of NMS cases in our hospital. Physicians from other non-specialised hospitals and private clinics in the area are not always aware the risk of NMS on withdrawal of antiparkinsonian drugs. Indeed, in 30 cases of Parkinson's disease, physicians stopped antiparkinsonian drugs because of psychiatric symptoms, dyskinesia, and the on-off phenomenon. These factors may have resulted in the accumulation of NMS cases in our hospital.

We were not aware that Japanese patients with Parkinson's disease are more prone to developing NMS when antiparkinsonian drugs are reduced. However, the possibility of genotypic differences between Western and Japanese populations is interesting,[2] and comparisons could usefully be made on the prevalence of mutations in parkin or other genes between these populations.

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Mesencephalic ischemia and Parkinson's disease

I read with interest the paper by Abe *et al*[1] on occipital and posterior parietal hypoperfusion in 28 Parkinson's disease (PD) patients without dementia. These findings suggest that there was a reduced regional cerebral blood flow (rCBF) in the intraparenchymal territory of the posterior cerebral arteries (PCAs) probably due to the presence of atheromatous plaques located in the distal end of the basilar artery.[2] Atherosclerotic changes are of considerable importance because they can cause stenosis and/or occlusion at the origin of the terminal (PCAs) or collateral (superior cerebellar arteries) branches, as well as of the posterior perforating arteries (PPAs).

Based on the fact that in situ the donor tissues of catecholamines are normally highly vascularised and by contrast in PD the rCBF is reduced in the neostriatum, from February 1988 to December 2002 we have used two surgical procedures to treat PD:[3–5] (1) transplantation of adrenal medulla into the putamen by a transinsular pathway, and (2) omental transplantation on the interpeduncular fossa, anterior perforated space, and insular cortex in 16 patients with moderate or advanced stages of PD. Thus, omental tissue revascularises to the catecholaminergic (dopaminergic and noradrenergic) nuclei, as well as to the surrounding structures, and moreover prolongs the survival of the graft implanted in the putamen. In all patients, neurological improvement was better during the first weeks after surgery than in the following months or years. Our third patient is the same case previously reported by us.[3] At present, 15 years postoperatively, she has only slight tremor on the left leg and does not require anti-parkinsonian medication. She occasionally receives 1 mg of clonazepam at night. Her quality of life is good and she manages the daily living activities similar to any normal woman of her age.

In conclusion, the vascular impairment described by Abe and colleagues supports the autopsy findings[2] and neurosurgical results.[3–5] Clinical data suggest that PD is initiated in the intraparenchymal territory of the PPAs caused by atherosclerotic plaques located at the mouths of these arteries. Therefore, we believe that Parkinson's disease is wrongly classified as a neurodegenerative disorder.

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Traumatic brain injury as a risk factor for Alzheimer's disease

In a recent systematic review of case control studies investigating head injury as a risk factor for Alzheimer's disease (AD), Fleminger *et al*[1] replicated the results of the meta-analysis by Mortimer *et al*[2] in males (OR 2.29; 95% CI from 1.47 to 2.00) but not in females (OR 0.91; 95% CI from 0.56 to1.47). Their findings support in males only an association between a history of previous head injury and the risk of developing AD, but the study could not review the relation between head injury and ApoE gene status as risk factors for AD.

The review by Fleminger *et al* was based on clinical studies alone and, as Wilson[3] emphasised, did not consider the nature or severity of the original head injury; and the results of the first retrospective autopsy study of the relation between closed traumatic brain injury (TBI), ApoE allele frequency, and AD[4 5] unfortunately were not mentioned. This present study has examined:

- the incidence of AD pathology in 55 consecutive autopsy cases (mean age 77.6 years, SD 7.1) with residuals of closed TBI lesions (old contusions in the frontal, temporal, or other brain areas)
- the frequency of TBI residuals in 53 age matched AD cases proven at autopsy.

In both series, ApoE was evaluated from archival brain material embedded in paraffin. The results were as follows.

In the TBI series, 12.7% (four males and three females) showed CERAD B (Consortium to Establish a Registry for Alzheimer's Disease) definite AD (Braak stages 5 and 6), and 9.1% showed CERAD B probable AD (Braak stages 3 or 4). TBI history dated back from 10 to 30 years before death; duration of AD ranged from four to seven years. Two of the subjects with AD showed ApoEε3/4, and the remainder 3/3 or 3/2; of the remaining 43 subjects without AD, three exhibited 3/4 alleles. The prevalence of AD (21.8%) in this small autopsy cohort was significantly higher than in either a recent large clinical series (3.3%)[6] or the general population over the age of 70 years (14%).[7]

In the AD cohort (all CERAD B or C, Braak stages 5 and 6), there was an ApoEε4 allele frequency of 30% (similar to other AD series). Residuals of TBI were seen in four brains (two males and two females, each 7.5% of the cohort), all four lacking the ApoEε4 allele. These data in small autopsy cohorts confirmed previous clinical studies suggesting that severe TBI is a risk factor for the development of AD, particularly in subjects lacking the ApoEε4 allele which is considered a risk factor for AD. No gender differences were found.

Irrespective of these data, we agree with others[1 3] that further work should consider population based cohorts and larger autopsy series of TBI and AD, in order better to elucidate the relationship between TBI, ApoE alleles, and the development of AD.

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The specificity of prescription patterns in secondary stroke prevention

We would like to comment on the important report by Landi and colleagues about the factors associated with a reduced likelihood of receiving secondary stroke prevention treatment[1] and present our own data. We have demonstrated that in community-dwelling patients with chronic atrial fibrillation, living alone or in rural areas, history of previous falls, and cognitive and functional impairments are independent factors that result in physicians prescribing aspirin instead of anticoagulants, thus disregarding the common guidelines for stroke prevention.[2 3] We have also shown that in some cases it does not mean malpractice.[3] In elderly patients, a geriatric assessment including a shrewd evaluation of the psychosocial conditions can guide physicians in the selection of the correct treatment, thus avoiding the risks related to anticoagulants in individuals at high risk of falls or with inability to comply with regular blood monitoring.[2–5]

Our data are only partially comparable with those of Landi and colleagues, since in their study a significant number of the reported undertreatment concerns aspirin and triclopidine, drugs that have an unfavourable risk–benefit ratio in comparison with anticoagulants, even when they are prescribed for individuals living alone, with a low education level and poor cognitive or functional performance. In these conditions, low compliance is not enough of a risk and does not justify undertreatment. As a matter of facts, in the clinical conditions described by Landi and colleagues, an ''ageist'' cultural background prevails without real clinical motivation.

The difference between the two sets of data suggests that physicians need to be taught to consider the complexity of the medical scenario and to distinguish incorrect prescribing patterns due to limitations imposed by cultural factors from the rational behavior of physicians who adopt a multidimensional model of care and avoid treatments commonly recognised as beneficial but burdened by a high cost–benefit ratio.

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Authors' reply

The data presented by Bellelli and Trabucchi confirm our findings suggesting that many older adults do not receive secondary stroke prevention treatment.[1] However, we really do not believe that our results indicate only an ''ageist cultural background without real clinical motivations''. Indeed, in our article we recognised that the decision of not to treat could not be considered as ''undertreatment'', but it may be related to the uncertainty about the cost-effectiveness of the treatment in a frail population. These doubts are not always unrealistic, especially among frail post-stroke elderly individuals, who characteristically have a high number and complexity of associated diseases, with a concomitant higher risk of drug interactions and adverse drugs events.[2] Furthermore, the reduced rate of treatment observed in our study is not only explained by potential risks in frail elderly patients, but also by uncertainties about the potential benefits.[3 4] In fact, the most important evidence of antiplatelet or anticoagulant medications after cerebrovascular accidents is substantially based on non-disabling ischaemic stroke. Evidence about the benefits of secondary stroke prevention is much more limited in the frail elderly population with severe physical and/or cognitive impairment. In this respect, it is important to underline the fact that the data presented by Bellelli and Trabucchi are based on a sample of community dwelling patients with atrial fibrillation, that ''per se'' is an indication to treat. In contrast, our study sample, which was based on patients receiving home care programmes indicating that an important and disabling health problem was in place, included a frailer population.[5] In this respect our results can not be generalised to all healthy community dwelling elderly individuals. However, we acknowledge that studies addressing the efficacy of secondary prevention treatment are needed, especially for frail and functionally impaired older individuals who have suffered a stroke.

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Relationship between stridor and sleep apnoea syndrome: is it as simple as that?

We read with interest the article by Hirayama *et al*[1] in which the authors, using an original imaging method, low field magnetic resonance fluoroscopic study, proposed that upper airway obstruction precedes laryngeal occlusion causing the stridor in patients with multiple system atrophy (MSA). This issue of nocturnal stridor in MSA is of great importance since it is a common cause of sudden death and a recognised prognostic factor in this disease.[2] It affects about 19% of patients as shown in our series and by others.[3] We feel that the relationship proposed between obstructive apnoeic respiratory events and stridor is not as simple as suggested by the authors and must be considered in light of classical standardised polysomnographic (PSG) data.

In our own series, 18 consecutive patients with MSA were assessed for night-time disturbances by all-night standard PSG with continuous synchronised audiovisual recording. Nocturnal stridor occurred in 10 patients and, except in one patient, was always accompanied by breathing disorders, mostly apnoeic, with or without significant oxygen desaturation. In four patients, obstructive sleep apnoeas (OSA) occurred without stridor, and one of these patients presented predominantly with central apnoea that also occurred while awake. Among the patients with stridor, four presented predominantly OSA and one mainly central apnoea. Mixed and prolonged apnoea, up to 53 s, was seen along with stridor in five patients and was isolated in two others. Episodes of mixed apnoea were typical in their occurrence as