Editorial

''Patients' choice''

M Rossor

Patients are becoming better informed and are increasingly involved in complex decisions of management. Patients are also becoming more involved in setting the medical research agenda. We know many major advances in medical science emerge from research that had no obvious clinical application; nevertheless, input into the direction of translational research is important. Equally it would be useful to have an input into the product of research—that is, publication. Bibliometrics reflect the interest and value to researchers themselves and are powerful drivers of further funding. A bibliometric that incorporates patient views, and we are all patients at some point, remains elusive. However, the journal would welcome patients' views on our publications and to that end we are introducing ''patients' choice''. We already have an editor's choice—a paper considered to be of particular interest or importance—that is freely downloadable from the website. The ''patients' choice'' will also be a free download. It will be an article thought to be of particular interest to patients and we have engaged the assistance of the *BMJ* Patient Forum to identify such articles. The decision to publish remains with the editors—like the editor's choice, the patients' choice is only made after the issue contents have been decided. We hope that authors will welcome this recognition of their papers and a wider readership will find it useful.

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White matter hyperintensities

White matter hyperintensities: a target for the prevention of cognitive decline?

D Leys, S Bombois

Lowering blood pressure might decrease the rate of cognitive decline in ϵ4 carriers and in subjects with white matter hyperintensities, a risk factor for cognitive decline

White matter hyperintensities (WMH) are frequent in apparently normal elderly subjects, in patients with vascular risk factors such as high blood pressure levels, in stroke patients, and in patients with either vascular dementia or Alzheimer's disease (AD). In this issue, the papers by Garde *et al* (***see pages 1289–91***),[1] Jokinen *et al* (***see pages 1229–33***),[2] and de Leeuw *et al* (***see pages 1286–8***)[3] provide evidence that WMH also influence cognitive functions independently of the underlying pathology. These three studies provide new information leading to potential strategies to prevent cognitive decline.

The more severe the progression of WMH over time, the more severe the cognitive decline in both AD patients[3] and normal elderly subjects.[1] This finding suggests that WMH should be regarded as risk factors for cognitive decline per se. Therefore, any therapeutic option that may slow the progression of WMH might help decrease the rate of cognitive decline in AD patients[3] and normal subjects.[1] As the major risk factor for WMH is arterial hypertension, blood pressure lowering drugs should therefore be tested first to examine this hypothesis in patients who already have WMH. When the role of cerebral atrophy is taken into account, the influence of WMH on cognitive functions remains significant,[2] suggesting that the results of previous studies[1–3] are not the consequence of cerebral atrophy which is frequently associated with WMH. After a stroke, WMH are also independently associated with cognitive impairment.[3] The hypothesis of de Leeuw *et al*,[3] that blood pressure lowering in patients with WMH might decrease the rate of cognitive decline in AD patients, is therefore valid also for stroke patients. However, white matter changes on CT scan in stroke patients are associated with an increased risk of stroke recurrence.[4] It is, therefore, difficult to evaluate the effect of blood pressure lowering drugs on WMH progression only: the reduction in stroke recurrences may account for some of the results, besides a possible reduction in the rate of progression of WMH.

The aim of the three studies[1–3] was not to explain why only some patients have rapid progression of WMH over time. Genetic factors might explain differences in the susceptibility of cerebral white matter to high blood pressure: in the Rotterdam study[5]: (i) APOE ϵ4 carriers had significantly more subcortical WMH than APOE ϵ3ϵ3 carriers, irrespective of their baseline levels of blood pressure;[5] and (ii) an ϵ4 allele and a high level of blood pressure were strongly associated with the presence of WMH, while hypertension alone or the presence of an ϵ4 allele alone were not.[5]

These radiological[1–3] and genetic[5] findings open a window for selective prevention of cognitive impairment in high risk subjects. The hypothesis that lowering blood pressure might be more beneficial in subjects with WMH and in ϵ4 carriers should now be tested in randomised trials.

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STN stimulation

STN stimulation and neuroprotection in Parkinson's disease—when beautiful theories meet ugly facts

P C Warnke

STN stimulation does not halt progression of Parkinson's disease

Repeated claims have been made that inactivation of the subthalamic nucleus (STN) is a neuroprotective measure.[1–3] It was postulated that by suppression of the glutamatergic STN, glutamate mediated excitotoxicity exerted on the substantia nigra could be reduced, if not abolished. The paper by Hilker *et al* in this issue (***see page 1217***) deals with this topic by looking longitudinally at patients who have undergone successful STN stimulation. The investigators have taken the approach of using objective functional imaging employing ^{18}F-DOPA positron emission tomography (PET), an established objective measure of biological progression in Parkinson's disease, which was then correlated with clinical progression. They were able to show convincingly that STN stimulation did not halt the progression of Parkinson's disease.

They have also shown that their technique of STN stimulation was effective both in terms of UPDRS improvement and in reducing L-DOPA or DOPA equivalent drug treatment, and was exactly within the range reported by other groups.

The PET approach to quantify disease progression will allow insights into disease biology and ways of modifying it. A critical point in using sequential PET studies is the reproducibility of quantitative ratios of L-DOPA uptake, especially in the light of huge interindividual differences in uptake in Parkinson patients. Furthermore, accurate repositioning of slices is another crucial point. Finally, patients were examined in the off-drug condition without STN stimulation but the follow up was done with deep brain stimulation turned on, though again in the off-drug condition. We have recently shown that a significant difference in dopamine transporter capacity, though not in dopamine uptake, can be seen between pre-STN stimulation and post-STN insertion but with stimulation turned off.[4] Thus electrode placement resulting in a ''microsubthalamotomy'' could have an effect on its own.

Nevertheless STN stimulation is like other traditional functional neurosurgical ablative techniques in producing symptomatic relief without affecting the biology of the disease.

What is the cause of the discrepancy between the experimental findings and this clinical study that rules out neuroprotective effects? The experimental papers used an artificial model of Parkinson's disease—that is, the 6-OHDA model which does not reproduce all the features of the disease. Furthermore in that model, STN ablation with kainic acid is used instead of STN stimulation to show the potential neuroprotective effects of STN suppression on the substantia nigra.

The paper by Hilker *et al* also raises questions about the focus of future neurosurgical approaches in Parkinson's disease. The investigators point out quite correctly that STN stimulation, which can be carried out bilaterally, has been found to be beneficial in numerous retrospective studies. However, it clearly only provides symptomatic benefit and therefore falls into the realm of traditional functional neurosurgical approaches such as STN ablation. In this context it is worthwhile asking whether the current prospective randomised controlled trial (the PD Surg trial) comparing bilateral STN stimulation with the best medical treatment is a wise investment of money. Very likely the study is going to prove the obvious. New attempts have been made by several neurosurgical groups to modify disease biology in Parkinson's disease and by doing so to achieve actual neuroprotection. These include attempts at the direct infusion of glial cell line derived neurotrophic factor (GDNF) using convection enhanced delivery, which seems to have long term effects in the same range as STN stimulation and looks very promising.[5 6] In addition, while still in the experimental phase the elegant approach of converting the excitatory glutamatergic STN by means of gene therapy into an inhibitory GABAergic nucleus—which is currently being tested in patients after successful results in an experimental Parkinson's model—also looks promising.[7 8]

Besides the worthwhile clinical information gained from Hilker's paper, another of its merits is to point out that, while STN stimulation is highly effective and beneficial in patients with Parkinson's disease, we should be looking for more sophisticated means of attacking the disease biology and hopefully modifying it.

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