PostScript

CORRESPONDENCE

Subthalamic deep brain stimulation for advanced Parkinson's disease: all that glitters is not gold

I read with interest the article "Behavioural disorders, Parkinson's disease and subthalamic stimulation" by Houeto *et al* and the accompanying editorial published last year in your journal.[1 2] One of the main conclusions of that study was that sometimes the reality cannot be completely reflected in a paper because many studies conducted to assess the efficacy of therapeutic interventions in Parkinson's disease focus on the motor aspects of the disease, while other aspects—cognitive or emotional, for example—are forgotten or insufficiently assessed by current rating scales such as the UPDRS. This is the case with most of the published studies related to deep brain stimulation (DBS). For this reason, I would like to add our experience with 18 patients operated on in our centre and included in the largest multicentre study conducted up to now.[3] In this study neither cognitive functioning nor quality of life were properly evaluated. Four of the 18 patients were prematurely withdrawn because of the occurrence of severe adverse events (two intracranial haemorrhages, one possible cortical venous thrombosis resulting in infarction, and one severe infection necessitating the removal of both DBS systems). In another patient with an impressive clinical result, one electrode was removed because of an infection, leading to a loss of efficacy in the contralateral hemibody. Three patients showed an improvement in motor function but also cognitive deterioration which was clinically relevant in one of them. Motor symptoms were significantly ameliorated in another patient; however, he developed postural instability with falls and mild cognitive deterioration with confusional episodes requiring institutionalisation. Another patient with Parkinson's disease and an associated gait disorder poorly responsive to levodopa, and with multiple lacunae on MRI, experienced a mixed result: whereas rest tremor and rigidity were markedly improved, the gait remained unchanged. Moreover, she started to have urinary incontinence and remained in a wheelchair. In two further patients, though DBS markedly improved all the cardinal symptoms of Parkinson's disease and levodopa induced dyskinesias, they both developed profound depression with apathy and social isolation.

In summary, with respect to the global clinical impression and quality of life, we can conclude that six months after the intervention DBS was highly beneficial in six patients. However, the remaining 12 patients suffered from a series of adverse effects that precluded a good clinical outcome, although an improvement in motor function was observed in many of them. Thus one can obtain an unrealistic impression of the impact of DBS in real life in this particular group of patients if only the motor aspects of the disease are analysed and summarised in a table.

Furthermore, as has been repeatedly noted in several congresses, around 25–30% of patients included in the multicentre study improved by less than 25% in the motor subscale of the UPDRS in double blind assessment, a result that can be considered unsatisfactory. For this reason, in this and other studies it would be important to indicate the percentage of patients improving more or less than a given level (for example, 25% in UPDRS III).

It should be emphasised that this was our initial experience and, in fact, it is quite similar to the one reported by Kumar *et al* with their initial nine patients.[4] Seven of them completed evaluations and four of them (elderly patients with advanced disease) developed operative complications. In spite of this, the reduction in off-period parkinsonism and the increase in daily "on" time were impressive. These investigators concluded that the motor benefits outweighed the adverse effects. This was also the case in some (but not in all) of our patients.

Finally, a recently published retrospective study of 211 patients conducted by Spanish teams showed that 19% of the operated patients failed to obtain the expected result.[5] Analysis of the possible reasons for these unsatisfactory results showed that the correct selection of surgical candidates (72% were elderly patients or had mild cognitive deficits, lacunae on MRI, or levodopa resistant symptoms) and definition of the target, along with surgical experience, were of crucial importance in obtaining the best results. The use of stricter selection criteria (a careful preoperative evaluation of psychiatric and cognitive function seems to be mandatory after the report by Houeto *et al*), and a larger surgical experience might improve these results. Therefore, I am convinced that at present the results are improving and will be even better in the future. I hope that the experiences of Houeto *et al*, along with those reported in this letter, will be useful for teams who are ready to start DBS procedures.

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Authors' reply

We thank Dr Linazasoro for his comments following the publication of our article.[1] The marked differences between our results and those of Dr Linazasoro are not related to the behavioural disorders we observed in some parkinsonian patients following bilateral subthalamic nucleus (STN) stimulation. Indeed, no reference is specifically made to psychiatric disorders.[1] As stated by Dr Linazasoro, the disappointing results obtained after neurosurgery in his experience are related to "the particular group of patients" included: the patients were old; the response of parkinsonian motor disability to levodopa treatment was poor; and there were axial motor signs poorly responsive to levodopa (gait disorder, postural instability, falls), cognitive impairment, and abnormal MRI (lacunae). It is therefore not surprising that the postoperative clinical outcome was poor, including severe adverse events. We agree with Dr Linazasoro that strict criteria need to be used to select appropriate candidates for neurosurgery. In our own experience, excellent results can be obtained provided that strict inclusion criteria are fully respected: the response of the patients to levodopa treatment must be excellent, which means that axial motor symptoms (that is, freezing, postural instability, hypophonia), known to poorly respond to levodopa, must be absent or moderate; cognitive and psychic impairment must also be absent, and the MRI normal.[2] Needless to say, the effect of the neurosurgery also depends upon the optimal placement of the electrodes within the STN, together with careful postoperative fine tuning of the electrical parameters.

In brief, the success of this neurosurgical approach to levodopa responsive forms of Parkinson's disease requires the expertise of a multidisciplinary team including neurosurgeons, neuroradiologists, neurophysiologists, and neurologists.

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Head injury outcome prediction in the emergency department: a role for protein S-100B?

I read with great interest the recent article by Townend *et al*[1] in which the authors studied the predictive value of protein S-100B in patients with head injury upon performance in the extended Glasgow outcome scale (GOSE). One important criticism is that the study was performed in patients with head injury defined as "any blow to the head causing a clinical diagnosis of head injury to be made, even if insufficient to cause definite loss of consciousness" and not only in patients with traumatic brain injury, which is defined

at least through loss of consciousness, amnesia, or postconcussion syndrome. Consequently, relevant abnormality of the brain even in minor traumatic brain injury was only detected in a few patients.

In addition, cerebral computed tomography (CT) was only performed in 15 of 148 patients. The extent of possible traumatic brain injury in the patients in the study by Townend *et al*[1] cannot be estimated. Patients with frontal contusion lesions in CCT and/or diffuse axonal injury were not separately identified in this study. Those patients are at high risk of having neuropsychological deficits and also frequently suffer from loss of insight. This may falsify the outcome measured by the extended Glasgow coma scale that was obtained by telephone interview only. Assessment by phone has limitations and cannot substitute a detailed neurological and neuropsychological examination that would reveal the above mentioned deficits.

In literature, CT controlled studies by Romner *et al*[2] (RIA), Ingebrigtsen *et al*[3] (RIA) and Biberthaler *et al*[4] (LIA-mat) calculated that an undetectable protein S-100B or protein S-100B below a cut off point at 0.1 ng/ml predict normal intracranial findings in CT. Herrmann *et al*[5] (LIA-mat) showed that an initial S-100B value above 0.14 ng/ml has a high predictive value for short-term and long term neuropsychological deficits in traumatic brain injury. A prospective study has not been performed yet.

Because in the study by Townend *et al*[1] measurements of protein S-100B were performed retrospectively without CT control or short-term or long term clinical monitoring, the study is of no clinical value.

Before implementation of a much needed neurobiochemical marker of brain damage in traumatic brain injury, there is a need for a prospective study of protein S-100B as a neurobiochemical marker of brain damage. This would include hospital monitoring of the patients with an initial cranial CT and MRI control as well as a short-term and long term neuropsychological follow up.

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Authors' reply

We thank Wunderlich for his thought provoking letter. The chief reservations expressed regarding the potential applicability of our findings seem to be that the entry criteria were too broad, that the measurements of protein S-100B were made retrospectively, that no CT control was performed, and that follow up might be biased. We will consider these points in turn.

The entry criteria were kept as broad as possible to enable the full cross section of patients with head injury to be evaluated. We are aware that traumatic brain injury is delineated more precisely according to the presence of a period of altered consciousness, particularly for research purposes. However, we were unable to find evidence in published literature that disability after head injury is confined to this group, although the rate would be expected to be higher than in those without such an alteration of conscious level. Also, there are no published data that we are aware of that demonstrate S-100B levels in those without altered consciousness after head trauma. We thought this would be of interest as clearly if there was a large proportion of this group with raised S-100B level and a uniformly good outcome, then its use as a prognostic marker would be limited by this false positive rate. For these reasons we consider our entry criteria apposite. By keeping patient selection as simple as possible, we anticipate that the least experienced practitioner would be competent to identify a patient in their practice that would be represented by our data. Our study, therefore, passes the test of applicability.

Wunderlich states that our S-100B measurements were made retrospectively. Our cohort was recruited prospectively. The blood samples taken for S-100B level estimation taken at initial assessment were analysed once outcome had been assessed. Blinding the outcome assessor to the S-100B level in this way was intended to reduce the risk of bias. Ours, therefore, is a prospective study. If the aim of Wunderlich's comment was to reflect the need for prospective validation of the cut off points we derived, then we agree, and are collecting data to that end.

The role of CT in the prediction of head injury outcome, or the relation between S-100B level and CT findings were not the aims of this study. CT data were included to demonstrate the infrequency of the use of this imaging modality in current UK practice, and thereby emphasise the role a serum marker might have. The purpose of CT in the emergent care of the patients with head injury is to identify lesions amenable to surgical intervention. Patients disabled after so called mild head injury often have normal CT scans, indeed our data suggest that currently in the UK many such patients will not even undergo such an investigation. There is also evidence that serum S-100B is a better predictor of outcome than Marshall CT classification after severe head injury.[1] We therefore foresaw little benefit in this study in correlating S-100B with CT abnormality. CT is likely to remain a poor surrogate for the entity we specifically sought to assess, namely neurological disability, which we scored directly using a validated tool. Routine CT, therefore, was not necessary in this study. Clearly a serum marker that, if "negative", could exclude a lesion requiring surgical intervention would be of immense value, but that was not the purpose of this study.

The possibility of the misrepresentation of outcome by patients with undiagnosed frontal contusions because of lack of insight was not considered when designing our study. That this effect might be exacerbated by telephone follow up is conceded. However, despite their limitations, we believe our arrangements ensured a reasonable follow up rate. This is not routinely the case in head injury studies. We also believe that the validity of our outcome measure has been demonstrated in published literature, and is also clinically relevant. The purpose of attempting to predict outcome as we have done is to identify those patients with head injury likely to benefit from intervention. If the assessment of that need is based on their inability to return to their previous life, rather than important but not so obviously relevant neuropsychological impairments, then a more compelling case can be made for such a programme to be resourced.

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Screening for variant Creutzfeldt-Jakob disease

The letter by Joiner *et al*[1] describes the lack of detectable prion protein (PrP) in three of four necropsy appendix samples from vCJD cases using a combination of immunocytochemistry and western blotting, thereby questioning the value of large scale screening of appendix tissue samples as an estimate of people who may be incubating vCJD. In our original description of PrP accumulation in the appendix before the onset of symptoms[2] we noted that PrP accumulation was focal and therefore we have used extensive sampling of the appendix for our study, resulting in a median of more than 24 secondary lymphoid follicles examined in each appendix case included. In addition we have used two different monoclonal antibodies to PrP and a very sensitive detection system,[3] to reduce the risk of false negatives. Using this approach we were able to detect lymphoreticular PrP accumulation in 19 of 22 vCJD necropsy appendix samples tested (two of the three negative samples had inadequate amounts of lymphoid tissue for assessment and would not have met inclusion criteria for our study[3]). In addition, of the three appendix samples removed before the onset of symptoms, the two removed in the 1990s were positive, and the third, removed in 1987 was negative.[3] All samples included in our study were removed between 1995 and 1999. The discrepancy between our findings and those of Joiner *et al*[1] may therefore result from our use of a more sensitive immunocytochemical approach and extensive tissue sampling.

While we accept that the sensitivity and specificity of screening tissue samples for lymphoreticular accumulation of PrP as a marker for vCJD is unknown, it seems to be a reliable approach in animals,[4] and given the lack of an alternative test and considerable uncertainty about future numbers of vCJD cases, we feel that such a study is justified. Our study has necessarily concentrated on appendix samples (as comparatively few tonsillectomy samples are archived), however we have recommended large scale screening of fresh tonsil tissue on a prospective basis,[3] which the Department of Health has now agreed to undertake.