Letter to the Editor

Rate of progression determines the clinical outcome after neural transplantation in Parkinson’s disease

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doi:10.1093/brain/awl112

Sir, I read with great interest the article by Piccini et al. (2005) analysing factors affecting the clinical outcome after foetal neural transplantation in Parkinson’s disease. A recent review on the same topic emphasized the role of immunological mechanisms, tissue manipulation before grafting and graft placement (Winkler et al., 2005), which can be of utmost relevance in explaining the negative final outcome shown by double-blind studies (Freed et al., 2001; Olanow et al., 2003). By using PET technology, Piccini et al. determined the amount of $^{18}$F-dopa uptake and $^{11}$C-raclopride binding in the grafted putamen, as well as in other areas that receive dopamine innervation, and correlated them with the clinical outcome during the first 2 years after transplantation. They found an increased $^{18}$F-dopa uptake in the grafted putamen in all patients. Patients with the worst outcome showed a parallel progressive reduction of $^{18}$F-dopa uptake in substantia nigra and median raphe region, as well as in the ventral striatum in which the uptake was reduced even before grafting. These areas are innervated by dopamine neurons located on the dorsal tier of the substantia nigra pars compacta and the ventral tegmental area. This suggests a continuing loss of dopaminergic neurons in substantia nigra despite a functioning graft that could affect the evolution of symptoms after transplantation. Thus, Piccini et al. state that the overall functional impact of dopamine neuron replacement is less pronounced in patients with more widespread forebrain dopamine denervation. The main conclusion of this study is that optimum symptomatic relief will most probably require tailor-made grafting procedures and multiple implantation sites based on detailed imaging of the denervation patterns in the individual patient. I fully agree with this conclusion. Furthermore, this study also lends support to the idea that rate of progression of Parkinson’s disease is determinant in the final outcome. Parkinson’s disease is a multisystem disorder (Braak et al., 2003) and, as time goes on, virtually every patient with Parkinson’s disease will be affected by damage to other areas of the brain, either dopaminergic or non-dopaminergic. The key question is at which rate.

A careful look at double-blind studies yields support to the role of rate of progression of Parkinson’s disease in the final outcome (for a more detailed discussion, see Linazasoro, 2005). Thus, interpretation of their results might be quite different if this variable would be taken into consideration. For instance, analysis of Olanow et al.’s (2003) study shows that age at onset and duration of Parkinson’s disease was quite different among the three subgroups studied. On one hand, patients included in the four donors group started with Parkinson’s disease at the age of 51.8 and scored 48.6 in the motor section of the Unified Parkinson’s Disease Rating Scale (UPDRS) after 8.2 years of evolution of the disease. On the other hand, patients receiving sham surgery had a disease starting at 43.8 years and scoring 51.5 in the UPDRS III after 14.2 years of evolution. This strongly suggests that patients included in this study have a very different rate of progression of disease. In contrast, the clinical characteristics of the six patients included in Piccini’s study and subjected to repeated $^{18}$F-dopa were quite similar to the group receiving sham surgery: Parkinson’s disease started at the age of 41 with a mean duration of 13.1 years and scored 40.5 in the motor UPDRS when off. The subgroup of eight patients subjected to both $^{11}$C-raclopride and $^{18}$F-dopa was comparable (Piccini et al., 2005). Therefore, these patients had a Parkinson’s disease with a relatively low progression rate (as a group), and, consequently, their clinical outcome was favourable.

A comparative view of the results of different studies using surgical approaches taking into account a ‘rate of progression index’ gives support to this idea (Table 1). This ‘rate of progression index’ is the resultant score obtained from the division of the score of the motor section of the UPDRS and the duration of Parkinson’s disease. Such an index does not exist and, therefore, it is necessarily arbitrary. Thus, general conclusions from clinical studies are difficult to draw, unless...
the role of disease progression is adequately addressed. In general terms, the lower the index, the better the outcome. If this is applied to Olanow et al.’s (2003) study, the group receiving transplantation from four donors would experience a mean change of at least 12.2 points in the motor section of the UPDRS, which could be significant. In keeping with this, it would be interesting to know if those patients included in the study by Piccini et al. (2005) who had the greater decrease in $^{18}$F-dopa uptake in the ventral striatum, substantia nigra and median raphe region and the less positive outcome also had a quicker rate of progression, although, presumably, it will be hard to reach such a conclusion given the small sample size.

Rate of disease progression can be seen as the expression of the relationship between the rate of neuronal loss in the pars compacta of the substantia nigra (and probably in other cortical and subcortical structures), and the strength of compensatory mechanisms. Rate of progression is influenced by age of onset as can be inferred from clinical and PET studies performed in young-onset Parkinson’s disease patients that suggest a lower rate in this group of patients (Khan et al., 2002; Thobois et al., 2003). This might be related to the power of compensatory mechanisms. Additionally, ageing may negatively influence the clinical course of Parkinson’s disease in several ways, including a disturbance or loss of compensatory mechanisms, as well as the presence of associated pathologies such as vascular lesions and atrophy. From this, it can be suggested that patients with young-onset disease have a slower rate of progression because they have stronger compensatory mechanisms and none of the pathologies usually associated with the ageing process. Conversely, these strong compensatory mechanisms may be responsible for the development of aberrant forms of plasticity resulting in the appearance of dyskinesias (Linazasoro, 2005). Interestingly, in double-blind studies the clinical outcome was better in patients younger than 60 in one study (Freed et al., 2001) and in patients with a lower disease severity (UPDRS III score < 49) in the other (Olanow et al., 2003). In these particular groups, clinical improvement was significant ($P < 0.005$).

In summary, rate of progression of Parkinson’s disease should be thoroughly analysed in the selection process of candidates, together with the presence of additional cerebral lesions. The study by Piccini et al. shows that a successful outcome of grafting depends on the simultaneous occurrence of degenerative and regenerative changes in the dopaminergic system. In other words, there is a continued loss of nigral dopamine cells, despite a functional graft. This continued loss occurs at different rate. Up to date transplantation procedures have been performed in patients with advanced Parkinson’s disease and motor complications refractory to conventional pharmacological treatments. And probably this is not the ideal situation. Transplantation ideally should be carried out when dysfunctional compensatory mechanisms staying at the striatal level are still reversible, a possibility more remote with the passage of time. This could reduce the rate of progression of Parkinson’s disease and add further clinical benefits to those purely derived from the increase in the number of dopaminergic terminals.

References

**Table 1** Comparison of results of different studies

<table>
<thead>
<tr>
<th>Progression index</th>
<th>Age</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanow (4 donors)</td>
<td>48.6/8.2</td>
<td>60</td>
</tr>
<tr>
<td>Freed*</td>
<td>38/13</td>
<td>50</td>
</tr>
<tr>
<td>Ma 1†</td>
<td>30.7/11.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Ma 2§</td>
<td>44/12</td>
<td>3.6</td>
</tr>
<tr>
<td>Hauser</td>
<td>50.8/18.2</td>
<td>2.8</td>
</tr>
<tr>
<td>Brundin</td>
<td>41.7/12.6</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Progression index: UPDRS III/Parkinson’s disease duration. aClinical data relative to patients younger than 60 (subgroup with significant improvement); †patients with runaway dyskinesias; §patients without runaway dyskinesias.