

## The curious incident of disability in multiple sclerosis trials

Inspector Gregory: "Is there any point to which you would wish to draw my attention?"

Holmes: "To the curious incident of the dog in the night-time."

Inspector: "The dog did nothing in the night-time."

Holmes: "That was the curious incident."

*Conan Doyle's The Silver Blaze*

There was a time when a neurologist could choose, rightly or wrongly, to downplay the significance of the first symptoms of demyelination: the "clinically isolated syndrome". No longer. Within minutes of an internet search, the person affected by, say, optic neuritis is faced with the possibility they might experience attacks of diverse symptoms, some indeterminate time away, and so develop "multiple sclerosis". And with that prospect come the spectres of disability, marginalisation, and frustrated ambitions. Sooner or later, come the questions: what does the future hold? Am I going to end up in a wheelchair? Handling this situation is a severe test of a neurologist's technical and pastoral skills. MRI brain scans can be useful; abnormalities consistent with plaques at presentation increase the risk of subsequent conversion to multiple sclerosis. For instance, 14 years later, nearly 90% of those who had an abnormal MRI scan will have developed multiple sclerosis, compared with less than 20% of those who had a normal MRI scan.<sup>1</sup>

Those people with a clinically isolated syndrome and an abnormal MRI brain scan ask: what can I do now to prevent further attacks and future disability? The answer is, embarrassingly, unclear. And the BENEFIT (Betaferon in newly emerging multiple sclerosis for initial treatment) trial<sup>2</sup>, reported recently in *Neurology*, helps not one jot or tittle. It is the latest of a trilogy of placebo-controlled trials, testing the efficacy of interferon beta to reduce the rate of conversion to multiple sclerosis in people with clinically isolated syndromes and abnormal MRI brain scans. Of the few drugs licensed to modify the course of multiple sclerosis, the innocuous safety profile of the interferons makes them the most appropriate to test on these mainly young, well people. CHAMPS (controlled high-risk subjects Avonex multiple sclerosis prevention study; n=383) of once-weekly intramuscular 30 µg interferon beta-1a (Avonex) was designed as a 3 year study, but was stopped early because of an interim analysis in favour of interferon so that only

262 patients (68%) generated the 2 year data.<sup>3</sup> The ETOMS (early treatment of multiple sclerosis; n=308) study of once-weekly subcutaneous 22 µg interferon beta-1a (Rebif),<sup>4</sup> and now the BENEFIT (n=487) trial of subcutaneous 250 µg interferon beta-1b every other day (Betaferon or Betaseron), were over 2 years.

The trial results are remarkably similar. Over 2 or 3 years, interferon beta reduced the proportion of people who developed a second attack of demyelination, and thus converted to multiple sclerosis, by about one third (placebo arm conversion rates: CHAMPS 0·50, ETOMS 0·45, BENEFIT 0·45 vs treated arms: CHAMPS 0·35, ETOMS 0·34, BENEFIT 0·28). A similar effect size was seen in the BENEFIT trial on those diagnosed as having multiple sclerosis by the more sensitive McDonald criteria, in which new MRI lesions can substitute for a second clinical episode (0·85 vs 0·69).

However, people with clinically isolated syndromes, just as those with multiple sclerosis, fear future disability not a change in diagnostic label. Does treatment with interferon beta reduce the long-term risk of accumulating disability? This key data is hard to find. It is omitted, despite being collected, from the BENEFIT and original CHAMPS papers. The ETOMS investigators were more straightforward: in their study interferon beta had no significant effect on the accumulation of disability. A similar lack of effect on disability was reported in the 5 year open-label extension study of the CHAMPS cohort.<sup>5</sup> This is not altogether surprising; the only effect established by a rigorous meta-analysis of the pivotal studies of interferon beta in relapsing-remitting multiple sclerosis was a reduction of relapse rate in the first year of treatment.<sup>6</sup> Under a sensitivity analysis, swayed especially by one trial that was stopped early, there was no significant effect of the interferons on the accumulation of disability.

There are several possible explanations for the dissociated effect of interferon beta on relapse rate and disability. The trials may simply have been too short, and the disability measures too insensitive, to identify a true treatment effect; support for this view comes from the finding of reduced MRI brain atrophy in the interferon arm of the ETOMS trial.<sup>7</sup> Or, much more worryingly, the mechanisms that underlie the acquisition of disability in multiple sclerosis may be independent of those that

cause relapses. Long-term data are needed. It is neither sensible nor safe to extrapolate from trials of a few years to effects on a life-long illness that usually starts in the third decade. 5 years ago, George Ebers wrote in his commentary on the ETOMS trial: "Unfortunately uncertainty on the key question of the long-term effectiveness [of the interferons] seems destined to persist for an uncomfortably long time."<sup>8</sup> We are no more comfortable today than then.

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I have received honoraria and travel expenses for speaking at meetings from Genzyme, Ilex Oncology, Millennium, Serono, and Schering. In addition, my department has received funds from Genzyme and Ilex Oncology to conduct investigator-led and sponsored studies of alemtuzumab in multiple sclerosis.

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## Deep-brain stimulation in Parkinson's disease

Deep-brain stimulation (DBS) for Parkinson's disease (PD) received yet another endorsement with the recent publication of Deuschl and colleagues'<sup>1</sup> large, randomised-pairs trial of subthalamic nucleus (STN) stimulation versus standard medical treatment. Despite many published studies of DBS in PD, few have been large, well controlled, or randomised using a medically treated control group for comparison. Furthermore, quality-of-life scales were used as the primary endpoint in Deuschl and colleagues' study in addition to standard motor scales for PD. Not surprisingly, surgically treated patients had substantially better outcomes at 6 months than did medically treated patients. In fact, improvements in scores on the Parkinson's disease questionnaire-39 after surgery were far greater than improvements in the scores noted in various clinical trials of antiparkinson drugs in which the questionnaire was used as a secondary response variable. Changes were understandably greatest in the motor aspects of the scale with little difference in the neurobehavioural components. Of note, in the paired analysis 36% of patients who received medical treatment showed greater improvements than their counterparts assigned DBS. Paired analysis of the off-medication motor component on the unified Parkinson's disease rating scale favoured the medically treated group in 27% of

pairs. Serious adverse effects, although infrequent, occurred more readily in the DBS group. Why did some of the medically treated patients do better than their DBS-treated counterparts and where should DBS now reside in the hierarchy of PD treatments?

First, not every patient benefits from stimulation and patient-selection criteria are still being refined. Movement disorder specialists lean towards offering DBS to younger, cognitively intact patients with clear-cut motor fluctuations and good response to dopaminergic treatment. We still have much to learn about the effects of DBS for other populations of patients and for specific PD symptoms. For instance, the effect of DBS on older patients, who represent most of the PD population, is not known because these patients are commonly excluded from research studies and might be more vulnerable to cognitive decline after surgery.

Second, despite improvements in motor function with DBS that far surpass measured improvements in most drug studies, there has been little documentation of improved emotional or cognitive status. Furthermore, worsening of non-motor symptoms such as depression, speech difficulties, and cognition have been noted in some patients treated with DBS.<sup>2</sup> Clearly, this is an area that needs further study as the neurobehavioural aspects of PD contribute immeasurably to long-term disability.