Dystonia: hopes for a better diagnosis and a treatment with long-lasting effect

Dystonias represent a group of heterogeneous neurological conditions characterized by sustained simultaneous co-contraction of agonist and antagonist muscles in one or more sites of the body. The resultant repetitive movements and abnormal postures can affect gait and execution of voluntary movements.

The pathophysiological mechanisms of dystonia remain to be fully elucidated. Not long ago, dystonia was commonly considered a manifestation of psychiatric disturbances and it has taken more than 40 years to recognize that dystonic movements originate from dysfunction within the basal ganglia circuitry. Findings from neuroimaging studies and physiological investigations clearly indicate that dystonia is associated with reduced inhibitory basal ganglia output, failure of cortical inhibition, abnormal sensorimotor integration, and maladaptive plasticity (Hallett, 2006). Over the last 20 years, many imaging studies using $^{18}$F-FDG PET, H$_2^{[15]$O$]$ PET and functional MRI have been performed in patients with different types of dystonia and have revealed widespread changes in cortical and subcortical activity, both at rest and during execution of motor tasks (van Eimeren et al., 2006; Neychev et al., 2011). Patients with primary dystonia caused by mutations in the DYT1 and DYT6 genes and asymptomatic gene carriers of these mutations, show an abnormal resting metabolic brain network, consisting of hypermetabolism of the basal ganglia, supplementary motor area and the cerebellum (Trost et al., 2002). Activation studies with H$_2^{[15]$O$]$ PET and functional MRI in both primary and secondary dystonia have shown abnormal activation patterns during motor tasks and following exposure to tactile stimuli (van Eimeren et al., 2006; Neychev et al., 2011). The most common findings are overactivity of the premotor and parietal cortices during motor tasks, which has been interpreted as evidence of cortical disinhibition. Although this evidence supports the view that dystonia is a basal ganglia disorder, cases where dystonia is secondary to psychological disorders and/or psychiatric illnesses, although uncommon, are well documented (Gupta and Lang, 2009). Unfortunately, since psychogenic dystonia often resembles the clinical characteristics of secondary dystonia, the correct diagnosis of the former can be extremely difficult, often resulting in unnecessary investigations and inappropriate treatments.

Assuming that the neurobiological substrates of psychogenic dystonia and organic dystonia are different, functional imaging techniques could potentially be used to differentiate the two conditions, but this has not yet been attempted.

In this issue of Brain, Schrag et al. (2013) used H$_2^{[15]$O$]$ PET to measure task-induced changes in regional cerebral blood flow in patients with psychogenic dystonia. Findings were compared with those of patients with genetically confirmed organic dystonia and healthy volunteers. All patients presented with fixed dystonia of the right lower limb. Regional cerebral blood flow was measured at rest, while holding a fixed posture, and during the execution of paced ankle movements of the right leg. In line with previous studies, patients with organic dystonia showed increased regional cerebral flow in primary motor, premotor and parietal cortices and a concomitant reduced flow reduction in the cerebellum. Interestingly, patients with psychogenic dystonia showed a completely opposite pattern of activation with reduced flow in the primary motor cortex and increased flow in the cerebellum and basal ganglia. These findings are important as they demonstrate for the first time that psychogenic dystonia and organic dystonia have distinct patterns of neuronal activity in cortical–subcortical areas, both at rest and during activation tasks. However, since H$_2^{[15]$O$]$ PET remains an expensive research tool and is not universally available, it would be valuable to reproduce the findings of this study by using more accessible techniques to measure changes in local neural activity during motor tasks, such as MRI and blood oxygen level-dependent (BOLD) sequences.

Despite the recent improvements in our understanding of the pathophysiology of dystonia, the pharmacological treatment of this condition remains challenging. Anticholinergic, benzodiazepines, tetrabenazine and newer-generation anti-epileptics are all useful medications in dystonic patients but they only provide partial remission of symptoms and the effects are generally short lasting. Botulinum toxin treatment, which induces chemical denervation of the affected muscles, is very effective in many cases and is the treatment of choice for most types of focal dystonia. In some patients, however, its effectiveness is only partial and can diminish after a few years of treatment.

Long-term electrical stimulation of the globus pallidus internus through chronically implanted electrodes is now established as an effective treatment for various types of dystonia in patients who do not achieve sufficient relief with pharmacological approaches. The use of deep brain stimulation for dystonia addresses, in particular, primary generalized or segmental forms, complex cervical dystonia, and tardive dystonia. However, very few longitudinal studies have been performed to assess how successful deep brain stimulation treatment is in the long-term.

Walsh et al. (2013) provide the longest follow-up of patients with cervical dystonia treated with globus pallidus internus deep brain stimulation reported so far. Briefly, 10 patients suffering from idiopathic cervical dystonia refractory to botulinum toxin and treated with bilateral globus pallidus internus were assessed in an open fashion at 1, 2, 3 and 5 years post-surgery. Seven patients had a 7-year follow-up and six of these had a further clinical assessment 9 years after surgery. Patients were assessed...
with the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), which provides reliable measures of torticollis severity, level of disability and dystonia-induced pain (severity of pain, duration of pain and disability due to pain). Video assessments from the preoperative period and the last clinical follow-up visit were also obtained and reviewed by two physicians blind to the time of assessment, providing some degree of objective measure in the study. The results indicate that globus pallidus internus deep brain stimulation in patients with cervical dystonia produces a significant symptomatic improvement, which is maintained at a mean of 9 years after surgery. In fact, after 9 years there was still a mean 55.5% improvement in severity, 63.5% improvement in pain and 82% improvement in disability with respect to baseline.

There is a degree of variability in individual responses to globus pallidus internus deep brain stimulation in this small cohort of patients with cervical dystonia, a finding that has been noted in previous studies (Andrews et al., 2010). In fact, ~20% of the patients have limited improvement (<25%) or even worsening of dystonia, despite correct positioning of the electrodes. This variability could be related to genetic heterogeneity of disease or to the characteristics of abnormal movements. Further studies including functional investigations of the neural correlates of globus pallidus internus stimulation in cervical dystonia and other forms of dystonia are needed to explain this variability of response and hopefully to identify those patients who will best respond to this type of treatment.

References


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doi:10.1093/brain/awt028