Generalised Dystonia in the Paediatric Setting: How is Deep Brain Stimulation justified?

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Introduction

On the 13th of January 2009, Guys and St Thomas Hospital in London reported that a patient of theirs, Thomas Melville-Ross, had recently undergone successful implantation of a Deep Brain Stimulation device. Thomas suffers from dystonia, and at the time of surgery was just five years old. Dystonia is a significant cause of severe childhood disability, but the application of this relatively new surgical technique, particularly in children, allows an unprecedented level of relief from dystonia.

The term “dystonia” is one that describes a vast range of clinical presentations. Although not the first to report the condition, Oppenheim coined the name in 1911 to describe a syndrome of alternating muscular tone abnormalities. Since then, the definition has become more precise; dystonia has more recently been described as a “movement disorder in which involuntary sustained or intermittent muscle contractions cause twisting and repetitive movement”. This definition is useful, as it does indeed describe the particular feature common to all dystonia syndromes. However, given the breadth of different types of dystonia, it can only be defined fully by explaining how it is classified.

Each individual dystonic syndrome can be classified in three ways – by aetiology, site and age of onset - any of which could be used as a starting point. Giron et al. choose to begin by explaining that dystonias may first be divided as either primary or secondary – that is, either genetically linked or idiopathic cases, or cases secondary to an external cause. Secondly, classification goes further by distinguishing between the different physical sites in which dystonia exists. There are many examples of so-called “focal” dystonia that affect a single region of the body, such as the hand or eyelid. If dystonia is not so localized as this, it may affect a segmented section of the body (segmental dystonia in, for example, Meige syndrome where blepharospasm is the key feature, but the jaw may become affected). Finally, the dystonia may be wider spread, to an entire side of the body (hemidystonia), or indeed the whole body as generalised dystonia.

The third and final classification uses the age at which the condition began in the patient. This is quite simply separated into early-onset and late-onset. The cut-off age that marks the boundary between early- and late-onset is blurred, with different authors suggesting a range of ages: Alterman and
Tagliati use 20 years, whilst the Dystonia Medical Research Foundation prefers 30 years in the information it lists for the public.

With dystonia being such a wide-reaching topic, this essay will consider just dystonia in the setting of paediatrics. In this context, I will assess the published evidence to draw conclusions about the use of an increasingly common neurosurgical technique, Deep Brain Stimulation (DBS). In order to do this, I will first explain the nature of paediatric dystonia. Secondly, I will explore the treatment options available to children to manage their dystonia, both medically and surgically. This is intended to set DBS in the context of its alternatives. Finally, I will discuss the use of DBS specifically, explaining something of the technical procedure but concentrating primarily on an examination of scientific evidence, to establish the safety and efficacy of DBS in children with dystonia. At this point it is important to note that whilst children may suffer from any pattern of distribution of dystonia, DBS is, for reasons explained later, normally reserved for generalised dystonia or, at the very most, hemidystonia. Consequently, discussion of pathophysiology and treatment methods in this essay will be mostly concerned with generalised dystonias in children that are, by definition, early-onset.

A background to generalised dystonia in children

The natural progression of dystonia in children unfortunately tends towards severe disability. An initial presentation will often be of a focal dystonia occurring earlier than ten years of age, which is likely to develop into a full generalised dystonia before the progression halts and the condition stabilises.

Secondary dystonia has, in its nature, an identifiable cause such as perinatal asphyxia or vascular malformation. Primary generalised dystonia remains poorly understood pathophysiologically, although a strong genetic component has been identified. This component is believed to be autosomal dominant in its inheritance pattern, but has a penetration rate of around only 30-40%; other genetic factors and environmental interaction are therefore likely to also play a significant role in the development of dystonia. Whilst the specific aetiology is unknown, it is recognised that 20% of early-onset dystonia patients carry a mutated gene (DYT-1) that mis-produces the protein TorsinA. This defective process may be linked to a disruption in dopaminergic mechanisms within the basal ganglia, which is a putative mechanism for the neuropathology behind DYT1-related dystonia.
Medical and Surgical Intervention

The treatments available to a child with dystonia should generally be considered to be unsatisfactory: in the end, medicine ultimately strives for a cure rather than symptomatic control but unfortunately this is just a distant thought in dystonia. As with many conditions, medical treatment is the mainstay, with surgical procedures attempting to continue where the physician can do no more. Alterman and Tagliati provide a useful algorithm that well illustrates the flow from a diagnosis of dystonia through medical care to surgery; it is adapted for inclusion here (Figure 1).

I have already explained that this essay can consider only generalised dystonia in its discussion of DBS; focal and segmental dystonias are normally dealt with more conservatively, particularly by local therapy with the notorious botulinum toxin, or Botox. Where focal dystonias can be tackled at the “superficial” end, generalised dystonia must be fought at the root, within the central nervous system. Referring to Figure 1, it is clear that the first step in the simplified management plan is to determine whether the dystonia is primary or secondary; this allows for exclusion of treatable metabolic causes. Once a primary aetiology is established, dopamine therapy should be trialed using L-Dopa. This step is important for two reasons. Firstly, it may elicit a diagnosis of dopamine-responsive dystonia (DRD), a form of dystonia caused by insufficient dopamine synthesis which can often be treated remarkably well with surprisingly small doses of levodopa. Secondly, a significant number of patients with non-DRD can also improve with levodopa, making its trial in everyone worthwhile.

When L-dopa therapy fails, other pharmaceutical strategies might be attempted. This can include anticholinergics, dopamine receptor agonists and benzodiazepines. However medical therapy is, unfortunately, littered with pitfalls. Anticholinergics, for example, can display convincing efficacy but can also have side-effects that must be carefully considered when prescribing to children. These include short-term memory deficit, confusion and behavioural changes, all of which could have a significant impact on a developing child in education; indeed, a study in the use of trihexyphenidyl to treat childhood dystonia related to cerebral palsy by Rice and Waugh noted side-effects in each of the sixteen participants, with two requiring hospitalisation.
Diagnosis of dystonia

Primary dystonia

Secondary dystonia

Treatable metabolic cause

Trial of L-dopa therapy

Anticholinergic therapy

Benzodiazepines or Baclofen

Intrathecal Baclofen

Tetrabenazine, DA agonists, CBZ, Topiramate

Deep Brain Stimulation

Figure 1 – The therapeutic pathway for generalised dystonia.
Adapted from Alterman and Tagliati, 2007.5

The gap between medicine and surgery is bridged by intrathecal baclofen pumps. These mechanical devices are implanted in the abdomen and administer intrathecal baclofen constantly; they have produced some results showing a fairly good therapeutic value.17. Unfortunately, this strategy brings with it the downsides of both surgical and medical therapies: there are the admittedly small but nevertheless significant risks and complications of surgical implantation, combined with a host of technical and medical difficulties. These are listed by Albanese et al. and include baclofen side-effects, infection potential and regular procedural requirements such as refilling the pump.18

Moving away from medical options, surgery has a fascinating history in the treatment of dystonia. The evolution of surgery for dystonia allegedly stems from an operation performed by pioneering neurosurgeon Irving Cooper. Cooper, ordinarily a deft and reliable surgeon, accidentally severed the anterior choroidal artery of a patient on whom he was performing a pedunculotomy for symptomatic
management of Parkinson’s Disease. He was forced to abandon the procedure but noticed that when the patient awoke, his tremor had ceased.\textsuperscript{19,20} This led the way to ligation of the anterior choroidal artery as an actual treatment for Parkinsonian tremor,\textsuperscript{21} and eventually thalamotomy for the treatment of dystonia in the 1960s.\textsuperscript{22} It is essentially a refinement of these earlier neurosurgical techniques from which the modern technique of DBS arose, all but consigning thalamotomy for dystonia to the pages of outdated textbooks.

So far, this essay has sought to reach a point at which the use of DBS in treating generalised dystonia in children can be examined. I have laid out a background of dystonia and its particular features in childhood, and in this section have provided the details of medical alternatives to surgical DBS. Next I shall consider DBS in detail, examining its application in children with dystonia and whether its risks can be justified in the face of the medical alternatives.

**Deep Brain Stimulation**

DBS is currently the most powerful tool in the surgical treatment of dystonia, as well as in a number of other neurological conditions. Put simply, it is a surgical procedure by which electrodes are inserted permanently into the brain, where their electrical activity can be controlled in order to alleviate the cramping contractions of dystonia. It has been used in some form since as early as 1987, to treat the tremor associated with Parkinson’s Disease.\textsuperscript{23} Perhaps understandably, DBS is cautiously regarded by some outside the medical world as surgery that “sounds like a form of fiendish torture”.\textsuperscript{24} The procedure itself involves the image-guided insertion of stimulating electrodes into a specified area of the brain. For dystonia, this area is the globus pallidus interna (GPI), which is the cerebral region primarily responsible for outflow tracts of the basal ganglia. It remains unclear as to why a stimulating electrode within the GPI should be able to relieve spasmodic contractions that characterise dystonia. Dostrovsky suggests that their action is not actually stimulatory \textit{per se}, but rather inhibitory, although he readily admits to the complexity of the neuronal pathways involved, and that much more specific work is needed if we are to fully understand the underlying process behind DBS in dystonia.\textsuperscript{25}

At this point it is worth noting that for generalised dystonia, the procedure would likely be bilateral, targeting both the right and left GPI. The electrode insertion is usually carried out stereotactically using
a head-frame, or more recently, using specialized frameless devices. A number of days after electrode insertion, the procedure is completed by attaching the electrodes to leads running down the neck and connecting to a battery-powered generator situated in a subcutaneous pocket, normally in the chest wall, or abdomen. In Parkinson’s Disease, the effects of DBS are almost instantaneous; in dystonia it often takes weeks.

The above account is a distinctly simplified version of the process of DBS implantation: the technical details are beyond the scope of this essay. It is, though, easy to see that DBS is a precise technique yet one for which the potential for complication is high. In order to answer the question of how DBS can be justified in the treatment of paediatric dystonia, a concept familiar to all medical practitioners must be addressed: risk versus benefit. Cooper complained in 1981 about the dilemma of choosing between the risk of a disease and the risk of a surgical operation. In assessing the use of DBS in childhood, the same dilemma is inevitably reached. To that end, this essay will first consider the risk of the disease, or rather, the potential benefit of the procedure. Secondly, it will consider the risk of the operation – that is, the risk of complications both minor and major, and assess their significance. It is if the benefit of DBS in children outweighs the risk, that DBS can be considered justified in its use.

Unfortunately, there is a distinct lack of good-quality, large-scale studies on the efficacy of DBS in dystonia, particularly in the paediatric field. This is almost certainly due to the relative scarceness of firstly DBS for dystonia as a procedure (just nine centres currently offer it for children in the U.K.), and also of early-onset generalised dystonia itself in the UK, particularly when compared to other candidate diseases for DBS, such as Parkinson’s Disease. However, the data that has been published shows an overwhelmingly positive response to DBS in a therapeutic context.

The first of these studies worth considering is from Parr in Oxford, who took just four patients, between the ages of eight and fifteen years old. With DBS, all of these children saw convincing, and occasionally dramatic, reductions in the severity of their disability (judged by the Burke, Fahn and Marsden Dystonia Rating Scale (BDMDRS), to be a mean improvement of 56%), and a consequent gain in independence over six months postoperatively. Alterman produced similarly pleasing results with a larger study group of fifteen, although only eight of these were under 21 years at the time of surgery. The study revealed the mean improvement in severity of disability over the entire cohort to be
75% at one year post-operatively; however, if just the young patients are taken, their mean improvement is as high as 97% after one year. A number of other studies continue to show beneficial effects of DBS in the treatment of children with early-onset generalised dystonia, including Zorzi’s work (where n=12 and mean improvement in BDMRDS score is 44.8%). As an additional point, Alterman’s study showed that possession of the DTY-1 genetic mutation is no indicator of clinical outcome with DBS.

Whilst the evidence that is available suggests that DBS can have great potential, it must be used with caution in order to account for the potential of any complications. Complications are an important consideration in all surgery; however, children bring with them particular problems that may increase surgical risk. Hariz provides a comprehensive list of potential issues in any DBS procedure, all of which apply to surgery in childhood; the list is summarised in Table 1. Vidailhet et al. conducted the first multi-centre study into the safety and efficacy of DBS, and were convinced by their findings of the safety of DBS. Their study only reviewed twenty-two patients, and of these there were five adverse reactions amongst three of the patients. Fortunately, these were resolved with no permanent consequences, which allowed Vidailhet to conclude that DBS is a safe treatment, given appropriate patient selection. These results in adults, however, cannot be automatically transferred onto children without taking into account a few important issues that may make children more prone to complications. These include the fact that, of course, children are physically smaller, requiring greater surgical precision and finer equipment and electrodes. Children also continue to grow after surgery, which may mean they outgrow electrodes or leads, making electrode fracture and lead disconnection more likely. Finally, as Parr remarks, children are more likely to take part in rough activities, such as sports or “sliding downstairs” which can put too much strain on the DBS system. However, with appropriate care from both the surgeon and the patient, risks can be minimised.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Complication</th>
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<tbody>
<tr>
<td>Pre-operative</td>
<td>◆ Inappropriate patient selection</td>
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<tr>
<td></td>
<td>◆ Imaging complications e.g. resulting in misalignment of head and frame.</td>
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<tr>
<td>Operative</td>
<td>◆ Traumatic complications of electrode insertion e.g. severe haemorrhage, paralysis.</td>
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<td></td>
<td>◆ Infection.</td>
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<tr>
<td></td>
<td>◆ Misplacement of lead/electrode.</td>
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<tr>
<td>Post-operative</td>
<td>◆ Infection.</td>
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<tr>
<td></td>
<td>◆ Skin erosion over site of electrode-cable connection.</td>
</tr>
<tr>
<td></td>
<td>◆ Electrode fracture/displacement/failure.</td>
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<td></td>
<td>◆ Stimulation side-effects e.g. confusion, speech disturbance.</td>
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Table 2 – The main complications of DBS surgery, listed by the stage of the surgical procedure at which they may occur. Adapted from Hariz, 2002.31

Conclusion

In this essay, I have discussed the issues surrounding treatment of early-onset generalised dystonia during childhood, with the particular question of DBS in mind – how safe is it for children and is its use justifiable? Brain surgery in children will always be a sensitive issue. If it were not for the small absolute number of young patients with dystonia who receive DBS, it would be surprising that the topic had received such little interest from a specifically paediatric point of view. It is for this reason that evidence relating specifically to children must depend on small-scale work such as that described above, and individual case studies.33 Further work, with long-term followup and of as large a size as possible, in multiple centres, must be a high priority to those who use DBS in children.

Whilst there is a lack of child-specific data available, the information that does exist shows DBS to be a very promising intervention for dystonia in childhood, and the complications that occur are handled well. Bearing in mind the fact that, as discussed, children may face a higher risk of complication with DBS than adults, taking this added risk rather than waiting until the child is older must be justified. With respect to this, I take the view of Alterman,6,29 and others. That is the view that DBS is justified in children after the failure of medical interventions, despite the additional risk, on the grounds of a number of factors. Firstly, an early treatment provides earlier relief from the pain of generalised dystonia...
dystonia. Secondly, children may actually be better candidates for DBS than adults because their improvement post-operatively is likely to be greater: this could be due to the changes in plasticity that occur with development, or the fact that orthopaedic changes caused by chronic muscle tone have not yet become so severe. Alongside the results that do confirm children have a better post-operative outcome that adults, an interesting side-point is that their school achievement also increases.

When the surgeons at Guys and St Thomas operated on Thomas Melville-Ross at the end of 2008, they exposed the five-year-old to all of the risks that I have discussed here. However, the benefits that Thomas will almost certainly derive from DBS, and the difference that it will make to his developmental processes, must surely justify those risks. DBS is a long way from being a cure for dystonia, but for many children with dystonia and their families, this neurosurgical advancement has been, quite literally, life-changing.

References


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