TOURETTE SYNDROME and DEEP BRAIN STIMULATION

Tourette Syndrome (TS) is a childhood neuro-behavioural disorder which is normally defined by the presence of at least one vocal and two motor tics, that starts before the age of 18 years, lasts longer than one year (Akbarian-Tefaghi, Zrinzo & Foltynie, 2016). In Australia TS impacts one in 100 school children, with about 500,000 cases per year (Victorian Government, n.d.). Tics are defined as sudden, short, intermittent, semi-involuntary movements and vocalisations that are preceded by a premonitory urge or impulse (Casagrande, et al., 2019). Most symptoms remit in early adulthood, but for around 20% of individuals' symptoms persist and have a detrimental effect both across the life span, and on their quality of life.

Alongside the tics there are often strong behavioural components with between 50% to 90% of patients experiencing psychiatric co-morbidities, particularly obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), deliberate self-injurious behaviours, and disturbances in mood such as depression and anxiety. OCD has been noted as the most debilitating aspect of TS from a social impairment standpoint (Porta, et al., 2016).

Traditionally TS is differentiated as pure-Tourette syndrome and Tourette syndrome-plus (Porta, et al. 2016). According to the DSM-V TS is now classified as a movement disorder under the neuro-developmental disorders section (Casagrande, et al., 2019). Deep brain stimulation (DBS) is only considered for patients with severe, chronic and disabling TS, known as medication refractory TS. This summary will briefly describe the most common deep brain stimulation targets, outcomes, and issues involved.

Despite the prevalence of TS, refractory TS is not common and thus there is difficulty in reproducing the large, multi-centre, randomized controlled trials necessary to improve and support knowledge around DBS. The most common brain regions studied in the literature

involving DBS are the centromedian-parafascicular region (CM-Pf) and the globus pallidus internus (GPi). Other target regions include the ventroanterior/ventrolateral thalamus, the globus pallidus externus, the nucleus accumbens and anterior limb of internal capsule, and the subthalamic nucleus (Testini, et al., 2016).

Improvements among patients in the CM-Pf target regions are quite variable, and some studies have attempted to determine whether it is the volume of tissue activated in the thalamus or the structural connectivity between the area stimulated that is associated with tic improvement. Brito, et al. (2019) concluded that it is not the volume of tissue in the thalamic area, but the pattern of connectivity between the region stimulated and the specific brain cortical areas, that was linked to patient outcomes. Stimulation of the ventroanterior/ventrolateral region has also been reported as a valuable option, with one study reporting a significant improvement in trait anxiety, quality of life, and global functioning (Huys, et al. 2016). A systematic review and meta-analysis by Baldermann et al. (2016) concluded that overall, the different brain regions resulted in comparable improvement rates, and was indicative of a modulation of a common network.

Improvements among patients in the GPi target region similarly have variable results around reduction in tic severity and obsessive-compulsive behaviours (Smeets, et al., 2016; Zhang, et al., 2016). Studies have noted the need for longer periods of time to measure improvements in this area, with one study evidencing no improvement in tic severity at the three-month period (Welter, et al., 2017). One of the larger pools comprised 48 patients who reported a 78% reduction in more than 50% of the Yale Global Tic Severity Rating Scale scores (Servello, et al. 2015).

DBS might be further complicated in patients with OCD. One case study which had reported significant improvement in both motor and phonic tics up to ten months, after which, there was a worsening of tics resulting from the patient's repetitive rotation of the right implantable pulse generator. These findings highlight the potential for residual obsessive-compulsive behaviours to undermine improvement (Pourfar, Budman, & Mogilner, 2015). Kisley, et al. (2014) in their systematic review and meta-analysis reported that the main outcome in the five studies that met their inclusion criteria was a reduction in OCD behaviours. Again, what is noted as lacking is adequate randomized controlled data and knowledge of the best target and stimulation settings. Trial design has similarly been identified as another reason why published double blinded randomized trials have failed to live up to the hype of open-label experience (in which 50% tic reduction is often reported). Within open-label reporting there exists variance due to, for example, variable GPi targeting, or stimulation adjustments post-surgery (Jimenez-Shahed, 2015).

Of concern is the possible adverse effects of DBS which include involuntary movements, mutism, impaired swallowing, nausea, anorexia, death, hematomas, hardware infection, hemorrhage, gait disturbances, acute psychosis, accidental switching off of stimulators, visual disturbances, libido increases, or erectile dysfunction. This list is not exhaustive and speaks to the point that is made generally across the literature, and that is the need for the strongly individualised and careful evaluation, together with the ruling out of possible somatoform disorders and treatment of co-morbidities, prior to consideration of DBS.

In conclusion, the use of DBS remains promising, but there still exists success and failures in multiple brain targets. Contemporary literature also points to the increasing experience with thalamic and pallidal DBS as paving the way to the development of closed loop approaches

(Martino, 2020). There remains the need for large multi-centre clinical trials, and until then evidence of an optimal approach remains unknown. Further collective evidence on this promising therapy for TS is available on a public website that sets out known outcomes. The International Tourette Syndrome Deep Brain Stimulation Public Database Registry can be found at

(https://tourettedeepbrainstimulationregistry.ese.ufhealth.org/#menu_patient_characteristics).

Martinez-Ramirez, et al (2018) reported that within 185 of these 205 patients that there was a reduction according to the Yale Global Tic Severity Scale of 45%. The most common targeted brain region was the CM-Pf region at 57%. As mentioned, DBS is not without adverse events which were experienced by 34% of these patients. Despite difficulties, the opportunities to enhance investigative efforts of DBS in TS are available and if pursued, might evidence a more robust tic and OCD reduction.

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