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EDITORIAL

Why so many deep brain stimulation targets in Tourette's syndrome? Toward a broadening of the definition of the syndrome

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Introduction

Tourette's syndrome (TS) is a neuro-developmental disorder characterized by simple or complex motor and sound tics starting before age 18 and that last for more than 1 year (TSA definition). TS can be considered as a sensory-sensitive-motor circuit dysfunction along with a strong behavioural component (Zapparoli et al. 2015a, b). It typically affects males more frequently than females (Khalifa and von Knorring 2003). The prevalence of tic disorder is about 0.85–1 % in the adults and up to 20 % in children according to (Robertson 2015). In the whole spectrum 90 % of patients present with at least one co-morbidity, such as obsessive–compulsive disorder (OCD), learning difficulty, poor impulse control, self-injury behaviour (SIB), attention-deficit-hyperactive-disorder (ADHD), non-obscene socially inappropriate behaviour (NOSI) and autistic spectrum disorder (Eapen et al. 2015; Robertson et al. 2015). Coexisting diseases are depression and anxiety symptoms (Robertson 2015). Tics are the main components in childhood, whereas OCD and other psychopathological traits are encountered more frequently in adolescence.

TS is considered increasingly a neurological disorder rather than a psychiatric disease. Traditionally TS is differentiated in pure-Tourette syndrome and Tourette syndrome-plus (Eapen et al. 2015). More recently five phenotypes have been identified by the London TS group. Phenotypes are (1) minimally affected class, (2) CMT (chronic motor tics) + OCD, (3) TS + OCD/OCB, (4) TS + OCD, (5) TS + OCD + ADHD (Grados and Mathews 2008; Eapen and Robertson 2015; Eapen et al. 2015). Based on our large experience OCD is probably the most debilitating and disturbing aspect of the disease, foremost from a social impairment standpoint (Servello et al. 2015), followed by sound tics and motor tics. Over the last decades, deep brain stimulation (DBS) has been considered an effective treatment option in severe TS patients' refractory to medication and by psychotherapeutic or cognitive behavioural therapies.

Management of TS patients

TS management is based primarily on Habit Reversal Training (HRT) (Woods and Miltenberger 1995; Piacentini and Chang 2005, 2006), Comprehensive Behavioural Intervention for Tics (or CBIT) (Piacentini et al. 2010; Wilhelm et al. 2012), and on pharmacological treatment (Robertson et al. 1996; Porta et al. 2008; Eapen et al. 2014). In particular for severe and refractory cases DBS represents a surgical option (Vandewalle et al. 1999; Visser-Vandewalle et al. 2003; Martinez-Torres et al. 2009; Servello et al. 2015). Early treatment is critical as it can ameliorate patients' quality of life and eventually natural disease course through mechanisms of neuroplasticity (Falowski et al. 2011). These treatment options can be used alone or in combination as add-on treatment, depending on each single case (Roessner et al. 2011).

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HRT and medications

HRT is a cognitive behavioural treatment that allows the patient insight into the disease, allowing acceptance and self -management of tics. The goal is to ameliorate the quality of life (Eapen et al. 2015). Pharmacological management is based on alpha-2 adrenergic agonists (clonidine), botulinum toxin, antiepileptic drugs (topiramate), anti-dopaminergic drugs and antipsychotic drugs (haloperidol, quetiapine, risperidone, pimozide) (Termine et al. 2013). However, these medications can have serious and multiple side effects, e.g. weight gain, Parkinsonism, dystonia and sedation (Weiden and Bruun 1987; Bruun 1988; Eddy et al. 2011).

Neurosurgery in TS

In 1970, Hassler and Dieckmann (Hassler and Dieckmann 1970) proposed thalamic ablation to control motor and sound tics in a small group of TS patients. Almost 30 years later, Vandewalle et al. (1999) reported a single TS case treated with bilateral DBS of the centromedian nucleus (CM) of the thalamus, the same target used by Hassler and Dieckmann decades earlier, and reported a 90 % tic decrease at 12 months follow-up. Contrary to DBS for Parkinson's disease, many more targets have been investigated in DBS for TS over the last 16 years (Hariz and Robertson 2010; Servello et al. 2015; Saleh et al. 2012); specifically, several different targets have been reported (Fig. 1). Based on double-blind studies the most robust and promising data comes from thalamic and pallidal stimulation (Ackermans et al. 2011; Kefalopoulou et al. 2015). Despite promising results (Saleh et al. 2012; Servello et al. 2015) DBS is still considered an experimental treatment option for TS; it has neither the Conformity European (CE mark), nor the US Food and Drug Administration (FDA) approval. It is of open label experience and used mainly as humanitarian device exemption in patients with severe debilitating and medication refractory TS (Motlagh et al. 2013), by respecting ethical and law conformity.

Several guidelines for DBS in TS management are reported

- 2006: USA/European Guidelines (Mink et al. 2006).
- 2008: Netherlands (Ackermans et al. 2008).
- 2009: Italy (Porta et al. 2009).
- 2011: UK (Cavanna et al. 2011).
- 2011: Europe (Muller-Vahl et al. 2011).
- 2012: Canada (Steeves et al. 2012).
- 2015: International (Schrock et al. 2015).

Inclusion criteria in DBS

TS patients are offered DBS if they are severely debilitated and refractory to any conservative treatment. The diagnosis needs to be confirmed by the neurologist alongside with the psychologist (in Italy exists a diploma for psychological medicine) or psychiatrist, who have to be experts in tic disorders. Severity of TS can be measured through specific clinical scales, the most used one is the YGTSS (Leckman et al. 1989) that measures the tics clinical and social impact. Another relevant tool is the Tourette Syndrome-Quality of Life Index (Cavanna et al. 2008) that is used in assessing TS patients' quality of life. Overall, a patient is considered particularly severe if YGTSS score is $\geq$35 (0–50). Comorbidities and coexisting symptoms need equally to be addressed (Robertson 2015): OCB/OCD are evaluated by the means of YBOCS (Goodman et al. 1989a, b), ADHD (Conners 1998) through CRS-R, depression through BDI-II (Beck et al. 1961), anxiety through STAI-Y-1, STAI-Y-2 (Spielberger and Vagg 1984). Another important issue to be considered during the evaluation procedure is not only the patient's, but also the caregiver's compliance, i.e. the exclusion of foremost behavioural disorders by the caregiver, which could influence negatively the long-term treatment procedure.

Exclusion criteria in DBS

Patients with severe medical, neurological, psychiatric or cognitive disorders can present a risk to every aspect of the surgical procedure. Abnormal brain MRI findings, major depression and/or acute suicidal tendencies at the time of DBS, body dysmorphic disorders, poor compliance and instable psychosocial circumstances are exclusion criteria.

Discussion

Based on our own experience DBS for refractory TS appears to be promising. On 48 refractory TS patients (11 patients excluded from final analysis) treated with DBS at our Galeazzi Institute (Milan, Italy), we noted in 27 patients a YGTSS score at the last follow-up visit that was less than 35 [pre-DBS YGTSS score of 72.12 (SD 14.48)]. In 29 cases a reduction of more than 50 % of the YGTSS score was observed (Servello et al. 2015). However,

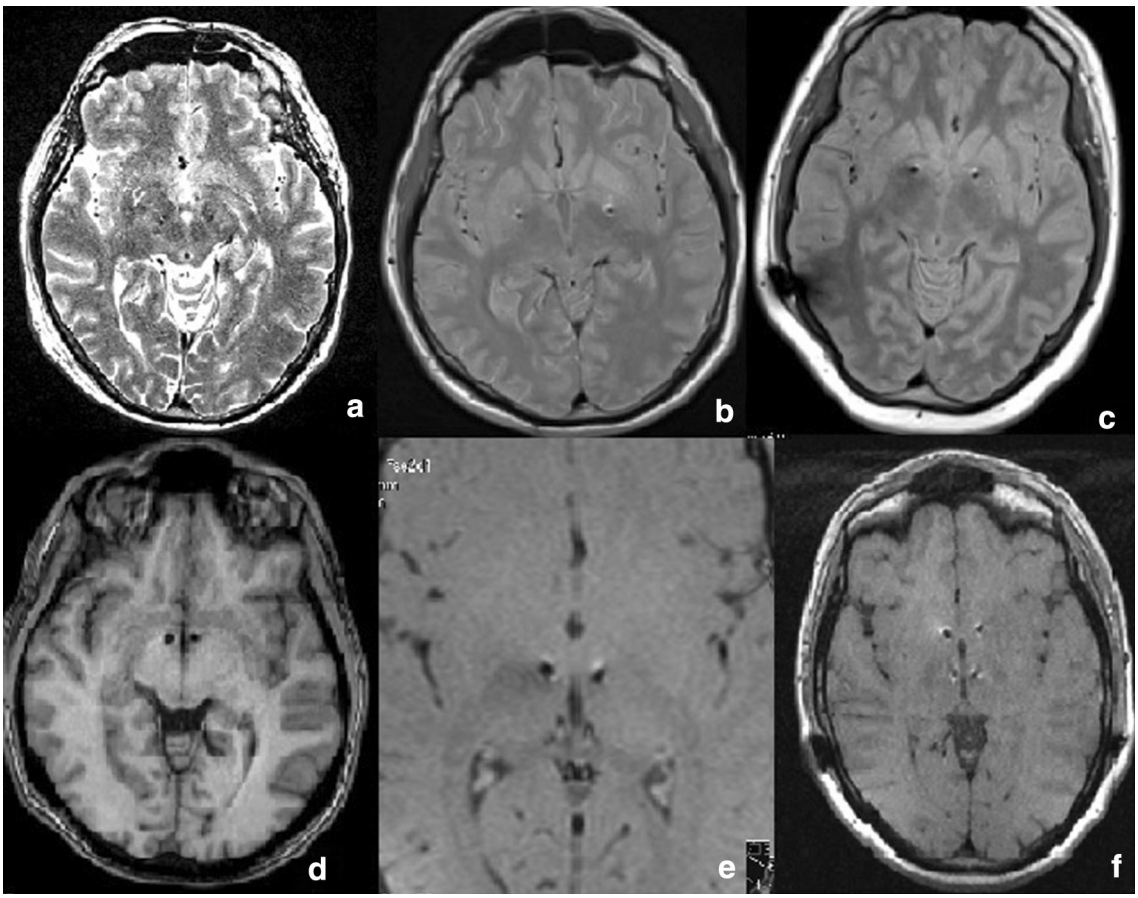

Fig. 1 Targets used in TS: **a** suthalamic nucleus (*STN*), **b** postero-lateral globus pallidus internus (*pl-GPi*), **c** antero-medial globus pallidus internus (*am-GPi*), **d** nucleus accumbens (*NA*), **e** thalamus, **f** dual stimulation

consensus is missing on multiple issues, foremost on the target choice, the definition of refractoriness (Porta et al. 2011), and on the age for the intervention. Yet, the issue as to the target choice might be even of secondary importance. A more important question might be if, despite the increasing tendency in the medical fields to standardise treatments, a consensus on target choice in TS is worthwhile? The reason therefore is that, TS is a unique complex spectrum of symptoms. Considering the important phenotypic variability of TS a single target choice in TS might therefore not be feasible and even be counterproductive. DBS should aim to treat the entire spectrum, including the plethora of associated comorbidities. Consequently, the selection of the target in every patient may result differently (Tremblay et al. 2015). The choice of the target depends, therefore, on the specific symptomatology of the patient. We use the thalamus in patients with a predominant tic symptomatology and low co-morbidity charge, while in patients with predominant comorbidity the preferred target is the nucleus accumbens/ventral striatum-ALIC. In patients with persistence of co-morbidities (OCD) despite thalamic DBS we stimulate the nucleus accumbens. We call this procedure as rescue surgery, i.e. a second surgery after poor results of the first surgical procedure. Patients with a high co-morbidity charge and important tic symptomatology a dual stimulation (i.e. thalamus and nucleus accumbens) is applied. Within this context of target choice, one should mind the existing interdependence between symptoms and also the complex interconnection between the various nuclei (Saleh et al. 2012). The largest experience comes from thalamic and pallidal DBS, which appear the most promising targets (Servello et al. 2015; Wardell et al. 2015; Kefalopoulou et al. 2015; Ackermans et al. 2011; Welter et al. 2008).

At our institution, we have a medication-guided DBS approach. We conduct a 6 months assessment according to the algorithm of "bouts of tics" (Peterson and Leckman 1998), i.e. tics fluctuations. Actually, this algorithm helps the clinician in distinguishing therapeutic efficacy of DBS from the natural disease history. Not the quantity of tic-forms, but their severity should guide the decision to consider DBS for treatment. Therefore, a patient with a single, but debilitating or severely disabling co-

morbidities, should be already considered a potential candidate for DBS.

Refractoriness is a further issue that needs urgently to be addressed (Porta et al. 2011). However, there is not even a clear differentiation between 'treatment-resistant tics' and 'treatment-resistant TS'. We consider a patient refractory to medication if there is a poor response to the pharmacological treatment after at least 6 months of treatment and/or side effects with at least two drugs encompassing (1) traditional and/or innovative antipsychotics, (2) catecolamine depletors, and (3) SSRI (Porta et al. 2011).

The age of the TS patient for DBS is greatly debated (Mink et al. 2006; Porta et al. 2009; Cavanna et al. 2011; Steeves et al. 2012). However, to delay DBS and waiting in a TS patient, who is refractory to conventional treatment, simply hoping his symptoms may subside in young adulthood, may not be solely unrealistic, but can also cause irreversible damages to the patient's present and future life. Offering DBS early on, as an eventual temporary treatment can bridge successfully this critical period of life (Zekaj et al. 2015). The DBS device could eventually be switched off or explanted when symptoms improve spontaneously over time. Our primary goal is not tic reduction per se, but always to reduce the social impairment due to TS, Social impairment is caused "in primis" by the aforementioned associated comorbidities, and only secondarily by sound tics, and only lastly by motor tics (Porta et al. 2011). The comorbid pathologies lead to a significant loss of quality of life, affecting to a great extent the private as the professional environments (Storch et al. 2007a, b). We have to remind again that 90 % of TS patients suffer from comorbidities, whereas pure tics are very rare (Robertson 2000).

Conclusion

Trials on DBS in TS are needed, in order to redefine this complex syndrome and to recognise comorbidities as part of the syndrome. Treatment priority should be the prevention/reduction of social impairment. DBS for TS should not be minimized as a tic treatment, but as a treatment for a complex bio-psycho-social disease. Tics for themselves can produce severe social impairment, but compromising are especially the associated comorbid pathologies, foremost OCD (Robertson 2015). According to the classification of the five phenotypes (Robertson 2015), many targets have been proposed and should be considered in DBS for TS (Servello et al. 2015). As there is a tailored pharmacological approach for each TS patients (Jankovic and Kurlan 2011) there has to be equally a tailored functional neurosurgical approach for each TS patient (Servello et al. 2015). A broadening of the definition of TS is therefore needed. Within this context DBS should be considered a treatment for both, i.e. tics and associated TS components and not only a treatment for tics. Therefore, a target choice based on consensus might prove counterproductive. Instead, a target selection based on a detail case-to-case evaluation may consequently prove in light of the complexity of this syndrome, a more efficient treatment approach.

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