



# The need for a proper definition of a “treatment refractoriness” in Tourette syndrome

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Gilles de la Tourette syndrome (TS) is a complex neuropsychological disorder usually characterized by both phonic and motor tics (Robertson, 2000; Porta et al., 2009a,b). The prevalence of TS reaches 50 per 10,000 in the general population (Leckman, 2002). Nevertheless, it is generally considered a “rare disease”: this is probably because of all the patients affected with TS only a minority suffers from a severe clinical picture. The syndrome demonstrates approximately a 10-fold higher incidence in children than in adults (Leckman, 2002), with a prevalence of up to 299 per 10,000 in children of age 13–14 years (Mason, 1998), while the onset of tics occurs at a mean age of 5–7 years (Freeman, 2000; Leckman, 2002). Especially because of this last issue, patients who are diagnosed with TS are often socially impaired. Even though the various degrees of severity of clinical manifestations of TS in certain cases allow a normal social functioning, when there is a social impairment this is often caused by tic manifestations. Tics are usually perceived as inappropriate, mimicking complex behaviors often of sexual nature. On the other hand, there is a widespread lack of information about TS so that people are unprepared to deal with these patients or to consider their behaviors as part of a disease. Moreover, behavioral comorbidities such as attention deficit-hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), and depression can further complicate the picture, and patients may be socially hindered because of both tics and behavioral abnormalities. Considering the complexity of such a variable clinical symptomatology in TS, the Tourette Syndrome Classification Study Group has introduced in their classification the subdivision between Definite Tourette Syndrome in which videotapes record the very clinical manifestations of the disease, and Tourette Syndrome by history, in which reliable caregivers (a family member

or a close friend) documents and describes the clinical features of the disease (Tourette Study Group, 1993).

A further difficulty in defining the specific clinical picture for the patient is that tics may change during the course of illness and new tics can issue (Du, 2010; Liao, 2010; Worbe, 2010). The development of diagnostic instruments that try to bypass the timing of the different clinical manifestations, such as the Diagnostic Confidence Index (Robertson, 1999), demonstrate the need for a sound description of such an ever-changing clinical picture.

As previously said, in a significant number of cases TS patients present also behavioral comorbidities. OCD is documented in up to 50% of patients in published experiences in Literature (Freeman, 2000; Robertson, 2000), while in our experience obsessive traits of personality can be demonstrated in up to 85% of patients. ADHD is present in up to 60% of patients in our series and in patients series presented in literature (Freeman, 2000; Robertson, 2000). Anxiety is documented in up to 40% of patients in literature data (Freeman, 2000; Robertson, 2000) while in our experience it presents in 50% of patients, while learning difficulties during school age present in 30% of TS patients both in our experience and in literature data (Freeman, 2000; Robertson, 2000). Some patients demonstrate a high grade of impairment in their social and working life (Neuner et al., 2009; Conelea, 2010; Du, 2010; Eddy et al., 2010, 2011).

Considering that a significant percentage of these patients may show a certain degree of improvement up to a complete disappearance of all clinical manifestations by the major age, deep brain stimulation (DBS) has classically been indicated for those patients failing to show a significant amelioration of symptoms during adulthood (Mink, 2006). On the other hand, it is during developmental age that clinical stigmata of the disorder cause the most of the damage, severely, and permanently altering the

social functioning of the patient, in some cases to an extent in which even after regression of symptoms the return to a normal social life is impossible. Moreover, DBS for TS seems to have significant incidence of complications and thus its indication must be evaluated adequately before proceeding (Servello, 2010). Conversely, drug treatment has been used when treating a young patient with a significant social impairment, but again, important adverse event may issue (Bestha, 2010).

Drug therapies involve antipsychotic medications that have been shown to be weighted by significant adverse effects that may persist during adulthood to a point that recently the need for more strict treatment guidelines has been required (Panagiotopoulos, 2010; Pringsheim and Pearce, 2010).

Considering the experiences presented in international literature, a structured protocol for drug therapies is usually not cited, and reports describe “maximum dose of established treatments” (Kuhn, 2007), “an inadequate response to at least two dopamine blockers or catecholamine depletors” (Maciunas, 2007), “failure of best treatment by medication (antipsychotics), or intolerance after a minimum of 6 months of treatment” (Welter, 2008).

Indication to treatment be it invasive or conservative should be considered on the basis of a definition of refractoriness to treatments proposed in the previous “step” of the algorithm.

Our guideline is that patients need to be observed in order to document (1) the most impairing feature of that specific TS picture – this also helps when determining the appropriate target for DBS, and (2) the evolution of the clinical picture – and thus the need for an invasive treatment on the basis of the severity of clinical manifestations and the need for specific medications on the basis of clinical manifestations. At our Institution (IRCCS Galeazzi, Milan, Italy) patients are followed with at least 2 years

of psychological therapy, and must show unsatisfying results (i.e., inadequate clinical response and/or side effects) with at least two drugs belonging to these categories: (1) traditional and/or innovative antipsychotics, (2) catecholamine depletors, (3) SSRI.

When considering DBS, our main goal (Servello, 2008) is to put the patient's quality of life at the base of a therapeutic algorithm involving DBS.

Results of the DBS choice for these patients are at best still experimental, and thus a definitive indication to treatment still has to be defined (Hariz and Robertson, 2010).

Ackermans (2008) reports different nuclei targeted with DBS for intractable TS: (1) the medial portion of the thalamus, at the cross point of centromedian nucleus (CM) with ventralis oralis pars intermedia (Voi); (2) the medial portion of thalamus, CM – parafascicularis (Pf); (3) the globus pallidus pars interna (GPi), posteroventrolateral part; (4) the GPi, anteromedial part; and (5) the nucleus accumbens (NAc) and anterior limb of internal capsule (IC).

A complete evaluation of the patient's quality of life must include the main complain of the patient and thus treatment should aim at treating that particular comorbidity or tic, and thus DBS target has to be tailored to the specific patient's clinical manifestation (Sassi, 2010).

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