Official Journal of the European Paediatric Neurology Society

Review article

Tourette Syndrome and comorbid ADHD: Current pharmacological treatment options

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ARTICLE INFO

Article history:
Received 10 September 2012
Received in revised form
30 December 2012
Accepted 26 January 2013

Keywords:
Tourette Syndrome
ADHD
Comorbidity
Pharmacological treatment
α-Agonist
Psychostimulants
Selective norepinephrine reuptake inhibitor

ABSTRACT

Background: Attention Deficit Hyperactivity Disorder (ADHD) is the most common comorbid condition encountered in people with tics and Tourette Syndrome (TS). The co-occurrence of TS and ADHD is associated with a higher psychopathological, social and academic impairment and the management may represent a challenge for the clinicians.
Aim: To review recent advances in management of patients with tic, Tourette Syndrome and comorbid Attention Deficit Hyperactivity Disorder.
Methods: We searched peer reviewed and original medical publications (PUBMED 1990–2012) and included randomized, double-blind, controlled trials related to pharmacological treatment for tic and TS used in children and adolescents with comorbid ADHD. "Tourette Syndrome" or "Tic" and "ADHD", were cross referenced with the words "pharmacological treatment", "α-agonist", "psychostimulants", "selective norepinephrine reuptake inhibitor", "antipsychotics".
Results: Three classes of drugs are currently used in the treatment of TS and comorbid ADHD: α-agonists (clonidine and guanfacine), stimulants (amphetamine enantiomers, methylphenidate enantiomers or slow release preparation), and selective norepinephrine reuptake inhibitor (atomoxetine). It has been recently suggested that in a few selected cases partial dopamine agonists (aripiprazole) could be useful.
Conclusion: Level A of evidence supported the use of noradrenergic agents (clonidine). Reuptake inhibitors (atomoxetine) and stimulants (methylphenidate) could be, also used for the treatment of TS and comorbid ADHD.

Taking into account the risk–benefit profile, clonidine could be used as the first line treatment. However only few studies meet rigorous quality criteria in terms of study design and methodology; most trials have low statistical power due to small sample size or short duration. Treatment should be "symptom targeted" and personalized for each patient.

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1090-3798/$ – see front matter
http://dx.doi.org/10.1016/j.ejpn.2013.01.005

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1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is the most common co-morbid condition encountered in people with tics and Tourette Syndrome (TS)[1]; it has been reported that 60%–80% of TS probands have comorbid ADHD.[2] About half of the individuals with chronic tics also meet diagnostic criteria for ADHD.[3] In referred tertiary clinical centers specialized on TS it has been reported that about half of the cases have comorbid ADHD, while 20% of children with ADHD presented comorbid tic disorder.

Furthermore, children with ADHD have an increased risk to develop comorbid tic disorders during their early school years. The Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA), and the Attention-Deficit Hyperactivity Disorder Observational Research in Europe (ADORE) studies reported the presence of tic disorder in 8–10% of ADHD patients.[4,5] Usually ADHD appears about 2–3 years before the tics, while in a smaller proportion of patients ADHD can be observed only after the tic onset; in addition, ADHD can continue into adolescence and adult life.

Comorbid ADHD can be accompanied by internalizing disorders, such as anxiety, as well as aggressive and oppositional disorders. Most studies suggest that ADHD is the main impairing factor on neuropsychological performance in comorbid children, while the presence of tics appears to have no or little influence on neuropsychological performance, particularly executive functioning.[6] Eddy et al. reported that high ADHD-symptom scores in TS were related to poorer QoL within the Self and Relationship domains.[7]

Rizzo et al. suggested that "pure" TS and "pure" ADHD differ in terms of behavioral and cognitive phenotypes while the combined disorder (i.e. TS + ADHD) appears somewhat to lie in between the two separate disorders from a behavioral point of view, but appears substantially closer to ADHD-only regarding behavioral and cognitive measures. TS + ADHD does not seem to be a more severe condition than ADHD alone.[8] TS and comorbid ADHD reflect a separate entity and not merely two-coexisting disorders. Banaschewski et al. suggested that some components of the etiological pathways of TS and comorbid ADHD may well be shared with the 'pure' conditions while others may be unique. It could be proposed that the comorbid condition would be a hybrid and combine the unique characteristics of both pure disorders. Suppression of tics may accentuate inattention in ADHD and attentional problems are correlated with the severity of tic, and inversely associated with the ability to suppress tics. In comorbid children, ADHD has been identified as more disruptive than TS but anxious and depressed symptoms were found to be equally or more strongly influenced by TD.[9]

The comorbidity between Tourette Syndrome and ADHD appear to have a complex pathogenesis and genetic factors can be implicated.[10] Genetic family study suggested that there may be two types of ADHD associated with TS. When ADHD precedes the appearance of tics, the conditions may be etiologically independent, but when ADHD follows the onset of tics they may be genetically related and ADHD may represent a variant expression of the underlying vulnerability genes for TS.[11] Abelson and colleagues (2006) identified a patient affected with TS and ADHD with a *de novo* chromosome 13 inversion, inv(13)(q31.1; q33.1.[12] More recently seven genes associated with TS were examined: DRD2, HRH3, MAOB, BDNF, SNAP25, SLC6A4, and SLC22A3 and it has been suggested that these genes have also been implicated in other disorders such as Attention Deficit Hyperactivity Disorder (ADHD), and Obsessive-Compulsive Disorder.[13]

Data on brain structure and neurochemistry are consistent with the notion that the two conditions may share similarities and differences. Hypofunction of catecholaminergic circuits, particularly those that project to the prefrontal cortex appear to be core features of ADHD,[14] whereas reduced volumes of the caudate nucleus, together with activation and hypertrophy of prefrontal regions seem to be core features of TS.[15,16] A significant loss of the normal globus pallidus asymmetry has been reported both in TS and ADHD patients.[17] Moreover, abnormal level of dopamine and glutamate have been reported in both conditions.[18] In details overactive dopamine transporter and alteration in phasic dopamine release could be responsible of tic and comorbid ADHD.[19]

The co-occurrence of TS and ADHD is in most cases associated with a higher psychopathological, social and academic impairment resulting from the negative impact of ADHD.[8,20] This co-occurrence causes clinical impairment, and the