Reviewer's report

Title: Tourette Syndrome and Learning Disabilities

Version: 2 Date: 4 March 2005

Reviewer: Jennifer Saltzman-Benaiah

Reviewer's report:

General
1. This article proposes to examine the differences between children with Tourette Syndrome (TS) who have a comorbid learning disability (LD) compared to those who do not. The comorbidity between TS and LD is an important topic, as both research and clinical experience suggest that many children with TS struggle in school. The authors were fortunate to have access to an international database containing an extremely large sample of children with TS and reported comorbid conditions. The authors point out that their inability to verify the diagnoses reported in the database is a limitation of the study, but argue that this may not have a significant bearing on the outcome because the results were highly statistically significant.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

2. Defining "learning disability"

The definition of LD used in the database is very vaguely defined in the paper, and one must consider that, depending on how this information (i.e., the diagnosis) was obtained, this may pose a rather significant problem in the interpretation of the results for several reasons:

The "clinicians" who provided data are "nearly all" physicians, who are unlikely to be trained in the diagnosis of an LD. Thus, the designation of LD must have come from another source, and this is unclear. Learning disabilities are typically diagnosed by Psychologists, and the diagnosis is always based on meeting specific criteria. Can the authors confirm that all of the individuals in the TS + LD category have undergone a psychological assessment leading to the LD diagnosis? If not, based on what criteria was the LD designation given by clinicians who reported this in the database? Was there a uniformly defined set of criteria to which each contributing clinician must refer? Again, if not, how can we be confident that the reporting of LD diagnoses has been uniformly applied and that the group is indeed representative of the LD population within TS?

This is particularly concerned since many children with TS have reported learning difficulties that may stem from circumstances and conditions other than an LD. For example, if it is the case that some clinicians reported children as having an LD based merely on a reported history of academic struggles, then it would be more appropriate to refer to this study as one which investigates children who have reported academic trouble compared to those who do not, rather than using the designation of "LD".

Evidence for the fact that the LD designation may not have been appropriately given by some clinicians is seen in the results wherein 11% of the individuals with LDs were also cited as having a developmental delay. These 2 diagnoses rarely co-occur, as children who have intellectual deficiencies are not typically also identified as learning disabled.

Since the authors use their findings to comment on the predictive value of certain variables in diagnosing LDs, and propose its value in leading to future research related to the prevalence and genetics of LD in TS, careful diagnosis is critical and not a minor limitation of the study.
Nonetheless, the study could still be interesting to readers as a preliminary indication of the high rate of academic difficulty in the TS population, and draws attention to some of the variables that may be related to this rate of presentation. It could be presented as a call for future research with tighter criteria.

Thus, it would be important to clearly define the criteria for using the LD label or to change the focus of the study to individuals with reported academic difficulties.

3. Information contained in the Results section would benefit from clarification.

The information presented in the result section is at some points confusing and would benefit from clarification. In the first paragraph of the results, the authors present many findings, but it is unclear if these refer to the sample as a whole, or just the TS + LD group? Please clarify.

In the second paragraph, the authors state that "table 1 shows variables with significant associations for TS + LD". It is assumed that they mean all of the variables considered are shown in Table 1, and that the p-values represent a significant difference between the two groups. Please clarify.

There are repeated references to the TS + LD group as being "more like to be/to have…". Although this likely refers to the fact that the TS + LD group has an even higher proportion of ____ (e.g., males, perinatal problems), individuals in both groups were more likely to be males, have perinatal problems etc. Although a technical point, this has important ramification for interpretation since the effects (e.g., more males) are quite apparent in both comparison groups, even when there was a statistical difference between the groups (see next point).

4. Many statistical differences between the groups are based on small differences.

Perhaps related to the extremely large sample size, group differences were highly statistically significant. Upon examination, however, many of the actual group differences were quite small. For example, 99% of the TS + LD group did not have a child with TS as compared to 97.4% of the TS - LD group. There are many examples of this in the paper, as reflected in the tables. In addition to statistical significance, it would be important to consider and comment on clinical significant/relevance of these findings. One might argue that a difference of a few % in one direction or another may not hold much clinical utility, especially when the base rates for these effects in TS are so high.

There are some findings in the study that do reflect larger differences that may hold true clinical utility (e.g., 10% more of TS + LD had perinatal problems compared to TS - LD). Further discussion of these points may be of interest to readers.

5. The authors have carried out a large number of analyses without correction for chance findings.

Given the large number of analyses (22 independent chi-square calculations + logistic regression), the chance of committing a Type I error is great. As such, it would be appropriate to implement a strategy to minimize the likelihood of Type I error from multiple analyses. Furthermore, the authors might wish to investigate statistical techniques that would allow them to take into account the known base rates for variables such as gender in TS when comparing the groups, to see if the findings in the TS + LD group are above-and-beyond what would be reasonably expected. The support of a statistician may be warranted depending on the expertise of the authors.

6. Further consideration of the clinical utility of the 5-variable model is warranted.

In the latter part of the paper, the authors focus on the 5-variable model that was determined through regression analysis to predict group membership. Again, the clinical utility of this model requires further clarification since most of these variables have strong trends in the same direction for both LD and non-LD groups, although more so for the LD in some cases. For example, both groups have a greater proportion of males to females, but more so in the LD group. Given the base rate for TS in males and females, is it reasonable to say that children who present with TS and are
male are at greater risk for an LD? Without clarification or explanation, the kind of conclusion could be misleading to clinicians.

The authors propose that these 5 variables could form the basis for screening LDs in a clinical setting. What about the other more obvious and likely predictive factors for LDs that were not captured in the database (e.g., early language delays, early academic struggles, family history). Surely the authors agree that such factors should form the basis for screening, with additional consideration given to the variables captured in their model, and not the other way around. This needs to be clarified in the paper.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
7. Page 4, paragraph 2, 1st sentence - not clear: "comorbidity is an important factor in…the longitudinal level of impairment from the disorder and comorbidity"
8. Page 5, Subject selection, "All subjects entered in the registry were required to meet the criteria…"
9. Page 7, paragraph 1, 1st sentence - total number of subjects was 5450, TS + LD had 1235 and T£ - LD had 3774. What happened to the other 441?

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Discretionary Revisions (which the author can choose to ignore)

None

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes

Declaration of competing interests:
I declare that I have no competing interests.