# Disentangling Tourette syndrome heterogeneity through hierarchical ascendant clustering

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**ABBREVIATIONS**

| | |
|---|---|
| ASD | Autism spectrum disorder |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition |
| HAC | Hierarchical ascendant clustering |
| OCD | Obsessive-compulsive disorder |
| YGTSS | Yale Global Tic Severity Scale |

**AIM** To explore the heterogeneity of Tourette syndrome as part of a neurodevelopmental spectrum.
**METHOD** Using hierarchical ascendant clustering based on tic symptoms, developmental milestones, and neurodevelopmental comorbidities, we analyzed the heterogeneity of Tourette syndrome phenotypes in a sample of 174 children and adolescents with Tourette syndrome referred to a tertiary university clinic.
**RESULTS** The model yielded three distinct clusters characterized as follows. In cluster 1, we found many neurodevelopmental comorbidities (including intellectual disabilities, autism spectrum disorder, attention-deficit–hyperactivity disorder [ADHD], and learning disabilities) and academic impairments. In cluster 2, patients had no other neurodevelopmental comorbidities. In cluster 3, patients had higher intelligence, a high frequency of attentional impairment, school problems related to both ADHD and unspecific attention difficulties, and handwriting problems related to the tics themselves. Interestingly, clusters did not differ in terms of family history or anxious-depressive comorbidities. The only other differences that emerged were related to prenatal or perinatal risk factors (more represented in cluster 1) and treatment profiles (higher rates of stimulants in cluster 1).
**INTERPRETATION** We conclude that from a phenotypical perspective, Tourette syndrome is a heterogeneous syndrome with at least three main clusters that may help in addressing the etiological basis of Tourette syndrome and specific rehabilitative and therapeutic approaches.

Tourette syndrome is a developmental, neuropsychiatric disorder characterized by multiple motor tics and one or more phonic tics lasting at least 1 year, with onset during childhood or adolescence.[1] In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), Tourette syndrome belongs to the 'neurodevelopmental disorders' group, together with intellectual disability, communication disorder, autism spectrum disorder (ASD), attention-deficit–hyperactivity disorder (ADHD), and specific learning disorder. As evidenced by recent literature, it is likely that these disorders share common risk factors and etiopathogenic backgrounds.[2,3]

Comorbidities and coexistent pathologies occur in the majority of patients with Tourette syndrome and, more than the severity of tics, contribute to the psychological and psychosocial impairment observed in Tourette syndrome.[4] Recent studies based on data reduction quantitative methods, such as factor analysis, cluster analysis, and latent class analysis, have shown that Tourette syndrome should not be considered a unitary condition.[5,6] The aim of these studies was to define subgroups of Tourette syndrome coherent in terms of clinical manifestations, to better understand the etiopathogenesis, and develop more comprehensive therapeutic strategies. In Table SI (online supporting information), we provide a synthesis of all the studies that explored Tourette syndrome through quantitative data reduction methods in order to clarify in detail the shortcomings of these studies and to facilitate comparison between them. So far, only a few studies included comorbid neurodevelopmental disorders as variables in building subgroups. Moreover, these works analyzed groups composed of children, adolescents, and adults. Considering these findings, the aim of this study was to assess the co-occurrence of neurodevelopmental disorders in a Tourette syndrome clinical sample referred to a tertiary university clinic and to address whether hierarchical ascendant clustering (HAC) based on tic symptoms, developmental milestones, and neurodevelopmental comorbidities can

delineate more homogeneous subgroups of patients in terms of clinical presentation and eventually etiological background. In the data reduction analysis, we did not include non-neurodevelopmental comorbidities and known risk factors. Within various machine-learning algorithms, we preferred HAC to other methods of clustering (e.g. K-means) because HAC does not require the number of clusters to be defined in advance. In addition, to limit bias, we excluded adult patients. Based on previous reports suggesting that high comorbidity rates in Tourette syndrome may define a specific syndrome named 'Tourette Syndrome plus' by Packer,[7] we expected at least two clusters.

**What this paper adds**

- The clustering of Tourette syndrome based on comorbidity with other neurodevelopmental conditions reveals three clusters.
- A group of patients with Tourette syndrome show school difficulties related to non-specific attention and writing problems.
- Analysing only children and adolescents helps to distinguish between developmental comorbid conditions and coexistent disorders.

## METHOD

### Participants

The current study was based on a prospective clinical registry including patients from the French National Reference Center for Tourette syndrome at the Pitié-Salpêtrière Hospital enrolled between 2010 and 2016. For the current sample, we extracted data from all patients who met the following criteria: children and adolescents (all individuals <17y) who received a formal diagnosis of Tourette syndrome according to DSM-IV/5 criteria and who completed the multidisciplinary assessment. The flow chart of the patients included in the current sample is shown in Figure S1 (online supporting information).

### Ethical approval

We report standard assessment and care in a rare condition, Tourette syndrome, so an ethical committee was not needed. However, the database was declared and registered to the National Commission for Informatics and Freedom that approved the use of the database for research purposes (CNIL number: 1465872). Patients or their caregivers have given informed consent to the research and to publication of the results.

### Data procedures

A two-step procedure was routinely used to assess patients and record variables in the database registry.

First, all patients and caregivers received a multidisciplinary evaluation by a child psychiatrist, a neurologist, a neuropsychologist, and a social worker. The neurologist questioned prenatal and perinatal events, development milestones, and the child's health record, family medical history, and illness course (age at onset, treatment, and social and family impact). Tic severity was assessed using the Yale Global Tic Severity Scale (YGTSS), an instrument that provides an evaluation of the number, frequency, intensity, complexity, and interference of motor and phonic symptoms.[8] The child psychiatrist investigated early psychomotor development, oral and written language, and motor development including coordination. Based on screening questions from the Mini International Neuropsychiatry Interview for Children and Adolescents, the child psychiatrist searched for main axis-1 comorbidities. Diagnosis of axis-1 comorbidities (obsessive-compulsive disorder [OCD], anxiety disorders, depressive episodes, and conduct disorder) was based on DSM-IV/5 criteria.[9] For OCD, we differentiated between OCD, obsessive disorder without compulsions, and 'tic-like' manifestations (repetitive behaviours such as touching, counting, 'just right', and symmetry searching) based on screening questions derived from the Mini International Neuropsychiatry Interview for Children and Adolescents and the Yale-Brown Obsessive Compulsive symptom checklist.[10]

In a second step, patients suspected to have one or more comorbid neurodevelopmental disorders were evaluated through specific tests. Patients suspected of having ASD were assessed using the Autism Mental Status Exam, an eight-item observational assessment that structures the observation and recording of signs and symptoms of ASD.[11] Patients who scored more than a 5 on the Autism Mental Status Exam were then evaluated with the Autism Diagnostic Interview-Revised,[12] a semi-structured, standardized diagnostic interview administered to the caregiver that analyzes the patient's behaviour in three domains (social interaction, communication, and restricted repetitive behaviours). Patients suspected of having problems in oral and/or written language were examined by a speech therapist or a reading specialist through a battery of standardized tests adapted for French pupils, providing an evaluation of the main domains of spoken and written language (articulation, phonology, vocabulary, and syntax). In particular, written language was tested with the Batterie Langage Oral–Langage écrit–Mémoire–Attention[13] and Lecture de Mots et Comprehension-Révisée,[14] while spoken language was tested using the Évaluation du Langage Oral test[15] In case of suspected motor deficits or coordination impairment, patients were specifically assessed by an occupational therapist with a battery of quantitative and qualitative tests including the Movement Assessment Battery for Children,[16] the Vaivre-Drouet test for distal gnosopraxis motor function,[17] the Goodenough (Draw-a-Person) test,[18] the Piaget-Head test for right-left orientation,[19] the Frostig test for visual perception,[20] and the Concise Assessment Scale for Children's Handwriting writing test.[21] These tests permitted an assessment of the patient's motor skills in term of coordination, body mapping, spatial and temporal marks, facial motor function, praxis, laterality, and graphic abilities. The neuropsychologist screened for general cognitive deficits and attention problems. In cases of suspected cognitive deficits, patients were given the Wechsler Intelligence Scale for Children – Fourth Edition.[22] Patients suspected of having attention problems, after being tested with the Wechsler Intelligence

Scale for Children – Fourth Edition, were also assessed with the Test of Everyday Attention for Children,[23] a test designed to assess selective attention, sustained attention, mental shifting from one task to another, and capacity to inhibit verbal and motor responses. A diagnosis of ADHD, including both subtypes (prevalent inattentive and mixed), was based on both DSM-IV/5 criteria and Test of Everyday Attention for Children results. A third subtype of attention problems, unspecific attention deficits related to tics, was defined to identify all patients with a clinically remarkable deficit of attention that, based on the neuropsychological profile and clinical course (e.g. appearance at tic onset, correlation with tic intensity, improvement with neuroleptics rather than stimulants), was likely secondary to Tourette syndrome. Diagnosis of a specific learning disorder was based on the results obtained from the psychometric, language, and motor tests and the DSM-IV/5 criteria. Finally, the social worker investigated school problems and family characteristics.

### Variables and statistical analyses

The list of variables resulting from the two-step process, included in the HAC machine learning algorithm, is given in Table I. Most variables reported in the registry were dichotomous variables based on presence or absence unless it was a quantitative variable such as age or testing/scale scores. Given the multidisciplinary sources of patients' assessments, we used a consensus multidisciplinary method for variables that were estimated by multiple sources. This process was used for OCD, ADHD, attention deficit, visual spatial impairment, learning disabilities, and developmental history.

All statistical analyses were performed using the statistical package R version 2.12.2 (R Foundation for Statistical Computing, Vienna, Austria). The significance level, $\alpha$, was set at 0.05, and all statistical tests were two-tailed. Given our main hypothesis regarding neurodevelopment, we first used HAC to classify patients according to the neurodevelopmental variables (Euclidian distance, Ward criterion). The term 'cluster analysis' refers to a group of multivariate methods that, by placing similar individuals into the same category, provide an independent empirical confirmation of clinical subtypes and in addition could create different and potentially better classification systems.[24] Recently, HAC has been successfully applied to identify different clusters within tic symptoms.[25] Variables are listed in Table I and included age, sex, abnormalities in psychomotor development, tic-related variables, and all neurodevelopmental variables. The clusters of patients were compared on the variables that were included in the hierarchical classification to better define the meaning of the resulting clusters. Then, the clusters of patients were compared on the variables that were not included in the cluster analysis (perinatal variables, family history, other comorbidities, and treatment variables) (Table II). Fisher's exact test was used for the qualitative variables, and an analysis of variance was used for the quantitative variables (age at the first evaluation; age at tic onset; all YGTSS scores; all WISC scores; Autism Mental Status Exam score).

## RESULTS

### Sample characteristics

A total of 174 patients with Tourette syndrome were enrolled in the study. The demographic and clinical data on the study sample are shown in Table SII (online supporting information). Here, we briefly summarize the main characteristics of the sample. In total, 148 (85%) patients were male. The mean age at the first evaluation was 11 years 4 months (standard deviation [SD]3.4), and the mean age at tic onset was 6 years 2 months (SD2.7). Complications during pregnancy or delivery were found in 23 (13%) patients. Fifty (29%) patients presented with abnormal psychomotor development, including a significant proportion ($n$=21, 12%) showing a certain precocity in acquiring the main developmental milestones. A positive family history of tics was found in 61 (35%) patients. The mean total YGTSS score was 53.5 (SD15.77). With respect to neurodevelopmental comorbid conditions, a diagnosis of ASD was found in 24 (14%) patients, whereas 10 (6%) patients received a diagnosis of intellectual disability. Attention difficulties were found in 94 (54%) patients. With respect to attention deficit subtypes, 38 (22%) patients had attention problems related to tics, 24 (14%) received a diagnosis of the ADHD inattentive subtype, and 31 (18%) received a diagnosis of the ADHD combined subtype. Regarding language disorders, 23 patients (13%) presented with isolated articulation/motor problems, and 21 (12%) had more complex spoken language problems involving all language domains (phonology, vocabulary, and syntax). With respect to written language problems, we found handwriting problems related to tics in 24 (14%) patients, while a diagnosis of dysgraphia or dysorthographia was found in 45 (26%) and 19 (11%) patients respectively. Forty (23%) patients received a diagnosis of developmental coordination disorder. Finally, dyscalculia was found in 52 (32%) patients and represented the most common diagnosis among specific learning disorders. Regarding non-neurodevelopmental comorbidities, the most frequent were anxiety disorders ($n$=70, 40%), OCD ($n$=47, 27%), depressive episodes ($n$=40, 23%), and conduct disorder ($n$=44, 25%). In terms of treatment, 44 (25%) patients were hospitalized at least once. The most commonly prescribed medications were antipsychotics (especially aripiprazole), followed by stimulants in the case of comorbid ADHD.

### HAC based on neurodevelopmental variables

As specified in the 'Method' section, we used an HAC analysis to examine the heterogeneity of patients included in the sample. According to our main neurodevelopmental hypothesis, the analysis was based on the variables listed in Table I, which included age, sex, abnormalities in psychomotor development, Tourette syndrome variables, and all neurodevelopmental variables. Figure 1 shows the

**Table I:** Tourette syndrome as a function of cluster analysis and according to neurodevelopmental and tic variables

| | Cluster 1 (*n*=74) | Cluster 2 (*n*=37) | Cluster 3 (*n*=63) | *p* |
|---|---|---|---|---|
| Male[a] | 27 (86) | 26 (70) | 58 (92) | 0.012 |
| Age at first evaluation[b] | 11.1 (2.8) | 12.6 (3.1) | 10.7 (3.7) | 0.020 |
| Abnormalities in psychomotor development[a] | 35 (47) | 8 (22) | 8 (13) | <0.001 |
| Global psychomotor delay[a] | 9 (12) | 0 (0) | 1 (2) | 0.007 |
| Language delay[a] | 14 (19) | 1 (3) | 1 (2) | 0.001 |
| Motor delay[a] | 4 (5) | 0 (0) | 0 (0) | 0.078 |
| Age at tic onset[b] | 6.2 (2.7) | 6.4 (2.9) | 6.1 (2.4) | 0.887 |
| Intellectual disability[a] | 11 (15) | 0 (0) | 0 (0) | <0.001 |
| Any language problems[a] | 61 (82) | 3 (8) | 19 (31) | <0.001 |
| Articulation problems/stuttering[a] | 17 (23) | 3 (8) | 2 (3) | 0.002 |
| Oral language disorder[a] | 19 (26) | 0 (0) | 1 (2) | <0.001 |
| Written language disorder[a] | 57 (77) | 0 (0) | 19 (30) | <0.001 |
| Any attention problems[a] | 39 (63) | 0 (0) | 48 (77) | <0.001 |
| ADHD[a] | 19 (26) | 0 (0) | 12 (19) | 0.004 |
| Attention deficit without hyperactivity[a] | 15 (21) | 0 (0) | 8 (13) | 0.009 |
| Non-specific attention problems related to tics[a] | 12 (16) | 0 (0) | 29 (46) | <0.001 |
| Any psychomotor disorders[a] | 41 (56) | 2 (6) | 2 (3) | <0.001 |
| Developmental coordination disorder[a] | 36 (49 | 2 (5) | 2 (3) | <0.001 |
| Neurovisuospatial disorder[a] | 24 (32) | 1 (3) | 0 (0) | <0.001 |
| Orofacial coordination disorder[a] | 6 (8) | 0 (0) | 1 (2) | 0.106 |
| ASD[a] | 23 (31) | 0 (0) | 1 (2) | <0.001 |
| YGTSS motor score[b] | 16.1 (4.8) | 14.5 (4.2) | 16.4 (4.2) | 0.151 |
| YGTSS vocal score[b] | 11.8 (5.5) | 9.6 (4.2) | 13.1 (5.0) | 0.010 |
| YGTSS OI score[b] | 26.4 (8.6) | 23.1 (4.7) | 26.7 (9.5) | 0.124 |
| Coprolalia/copropraxia[a] | 27 (36) | 10 (26) | 22 (35) | 0.62 |
| Stereotypies[a] | 29 (39) | 6 (17) | 9 (15) | 0.003 |
| School problems[a] | 69 (93) | 1 (3) | 61 (97) | <0.001 |
| Dyslexia[a] | 24 (33) | 0 (0) | 1 (2) | <0.001 |
| Dysgraphia[a] | 41 (56) | 0 (0) | 5 (8) | <0.001 |
| Spelling[a] | 19 (25) | 0 (0) | 1 (2) | <0.001 |
| Dyscalculia[a] | 34 (46) | 0 (0) | 21 (33) | <0.001 |
| Handwriting problems related to tics[a] | 11 (15) | 0 (0) | 13 (21) | 0.015 |
| WISC-IV scores (*n*=76 available) | | | | |
| Heterogeneous WISC scales[a] | 55 (75) | 28 (75) | 44 (70) | 0.89 |
| High potential[a] | 0 (0) | 3 (9) | 14 (23) | 0.001 |
| Verbal Comprehension Index[b] | 100.5 (22.5) | 106.7 (23.4) | 114.4 (16.9) | 0.061 |
| Working Memory Index[b] | 90.9 (16.1) | 96.7 (20.0) | 102.9 (17.6) | 0.041 |
| Cognitive Speed Index[b] | 88.7 (18.7) | 103.7 (20.2) | 98.2 (18.5) | 0.062 |
| Performance Index[b] | 80.6 (21.6) | 93.4 (11.2) | 93.1 (15.9) | 0.034 |
| AMSE score (*n*=28 available) | | | | |
| AMSE[b] | 5.4 (2.2) | 4.0 (3.5) | 2.2 (0.7) | 0.004 |

[a]Number (%); [b]mean (SD). ADHD, attention-deficit–hyperactivity disorder; AMSE, Autism Mental Status Exam; ASD, autism spectrum disorder; OI, overall impairment; WISC-IV, Wechsler Intelligence Scale for Children – Fourth Edition; YGTSS, Yale Global Tic Severity Scale.

dendogram displaying the analysis results. Among the 174 patients selected, we identified three main clusters. Interestingly, the three clusters did not differ according to age at tic onset or tic severity as demonstrated by the YGTSS scores, with the exception of cluster 3, which showed higher scores in the YGTSS vocal subdomain.

Cluster 1 comprised 74 patients (42.5% of the entire population) presenting a more complex phenotype, with multiple comorbid neurodevelopmental conditions. In cluster 1, Tourette syndrome, communication disorders, developmental coordination disorder, intellectual disability, ADHD (both inattentive and mixed subtypes), ASD, and specific learning disorders tended all to co-occur with high statistical significance ($p<0.01$) with respect to both other clusters identified. In particular, cluster 1 included high rates of both spoken language and written language disorders. Equally, two of the subgroups of psychomotor problems we analyzed (developmental coordination disorder and neurovisual spatial problems) showed higher rates in cluster 1 with respect to other clusters. Finally, we found high rates of school problems in cluster 1. In particular, all the subcategories of learning disorders we analyzed (dyslexia, dysgraphia, and dyscalculia) and tic-related handwriting problems were found at a higher proportion within this cluster with the exception of dyscalculia, which was also found in high proportion in cluster 3.

Cluster 2 was composed of 37 (21.3%) patients who presented 'pure' Tourette syndrome. In this group, other neurodevelopmental conditions tended not to co-occur. Instead, patients belonging to this group showed high rates of comorbidity with OCD. Given the high rates of OCD found in the other clusters as well, it appears that OCD could be interpreted as a part of the 'transnosographic core' of Tourette syndrome with a common genetical background and overlapping clinical features. Patients in cluster 2 received their first evaluation at an older age than

**Table II:** Prenatal and perinatal risk factors, family history, non-neurodevelopmental comorbidities, and therapies associated with Tourette syndrome according to the three clusters

| | Cluster 1[a] (*n*=74) | Cluster 2[a] (*n*=37) | Cluster 3[a] (*n*=63) | *p* |
|---|---|---|---|---|
| Any pre- or perinatal risk factors | 14 (19) | 2 (5) | 6 (10) | 0.096 |
| IUGR | 1 (1) | 0 (0) | 2 (3) | 0.603 |
| Prematurity | 7 (9) | 1 (3) | 5 (8) | 0.495 |
| Other pre- or perinatal risk factors | 7 (9) | 1 (3) | 0 (0) | 0.024 |
| Any family history | 35 (48) | 18 (49) | 28 (44) | 0.892 |
| Family history of chronic/provisional tic disorder | 24 (32) | 16 (43) | 21 (33) | 0.498 |
| Family history of Tourette syndrome | 4 (5) | 3 (8) | 4 (6) | 0.853 |
| Family history of ADHD | 1 (1) | 0 (0) | 0 (0) | 1 |
| Family history of OCD | 6 (8) | 5 (14) | 4 (6) | 0.50 |
| Family history of ASD | 6 (8) | 0 (0) | 1 (2) | 0.106 |
| OCD | 30 (40) | 17 (46) | 20 (32) | 0.337 |
| Obsessive disorder without compulsion | 5 (7) | 3 (8) | 2 (3) | 0.486 |
| 'Tic-like' manifestations | 5 (7) | 4 (11) | 2 (3) | 0.279 |
| Anxiety disorders | 35 (47) | 11 (30) | 24 (38) | 0.219 |
| Depressive episode | 13 (18) | 11 (30) | 16 (25) | 0.324 |
| Conduct problems | 27 (36) | 4 (11) | 14 (22) | 0.014 |
| Hospitalization | 28 (38) | 4 (11) | 13 (20) | 0.005 |
| Medication | 60 (81) | 29 (78) | 52 (83) | 0.877 |
| Neuroleptics | 55 (74) | 29 (78) | 46 (73) | 0.883 |
| Stimulants | 31 (42) | 2 (5) | 15 (24) | <0.001 |
| Antiepileptics | 5 (7) | 2 (5) | 3 (5) | 0.915 |
| SSRI | 13 (18) | 7 (19) | 12 (19) | 0.962 |
| Medication efficacy | 33 (45) | 21 (57) | 27 (43) | 0.366 |
| Any psychotherapy | 52 (70) | 25 (67) | 37 (59) | 0.391 |
| Cognitive behavioural therapy | 9 (12) | 10 (28) | 9 (14) | 0.112 |
| Hypnosis | 2 (2) | 2 (6) | 1 (2) | 0.449 |
| Motor rehabilitation | 43 (58) | 4 (11) | 6 (9) | <0.001 |
| Speech therapy rehabilitation | 53 (72) | 3 (8) | 7 (11) | <0.001 |

[a]Number (%). ADHD, attention-deficit–hyperactivity disorder; ASD, autism spectrum disorder; IUGR, intrauterine growth restriction; OCD, obsessive-compulsive disorder; SSRI, selective serotonin reuptake inhibitors.

patients in cluster 1 or cluster 3 (median age at first evaluation: 12y 7mo).

Cluster 3 included 63 (36.2%) patients presenting Tourette syndrome associated with high rates of school problems related to the presence of ADHD (both mixed and prevalent inattentive subtypes) but also attention difficulties and handwriting problems both secondary to tics. With the exception of dyscalculia, patients in cluster 3 did not show high rates of specific learning disorders or other neurodevelopmental conditions. Rather, we found a certain precocity in developmental milestones with higher rates of high potential individuals. In terms of demographics, this cluster had the youngest age at first evaluation (mean 10y 8mo and the highest rate of males [92%]).

### Other variables according to neurodevelopmental clustering

Table II summarizes the variables (prenatal and perinatal risk factors, family history, non-neurodevelopmental comorbidities, and treatment variables) that were not included in the cluster classification according to each cluster. Regarding family history (whether limited to Tourette syndrome or other conditions), we found no significant differences between clusters. With respect to comorbidities other than neurodevelopmental disorders, we also found no differences in rates of anxious-depressive disorders across clusters. The only exception was for conduct disorder, which was more frequent in patients in cluster 1. Regarding prenatal and perinatal risk factors, we largely did not find any significant differences among clusters. However, patients in cluster 1 had significantly more perinatal issues (mainly caused by preterm birth). The main differences between clusters in treatment approaches included patients in cluster 1 having more frequent hospitalizations (required for the treatment either of tic symptoms or comorbidities) and requiring more rehabilitative interventions (both logopedic and psychomotor rehabilitation), during current lifetime but also in the early developmental period. A significant statistical difference was found in this group with respect to both other clusters for the administration of stimulants, but not for antipsychotics.

## DISCUSSION

### Main findings

The purpose of this study was to explore the heterogeneity of Tourette syndrome as a part of a neurodevelopmental spectrum. Using HAC based on tic symptoms, developmental milestones, and neurodevelopmental comorbidities in a sample of children and adolescents with Tourette syndrome, we identified three different clusters. Figure 2 provides a graphical representation of the three clusters according to the age at onset of comorbid neurodevelopmental disorders. Patients belonging to the cluster 1 group presented the most complex phenotype, with multiple co-

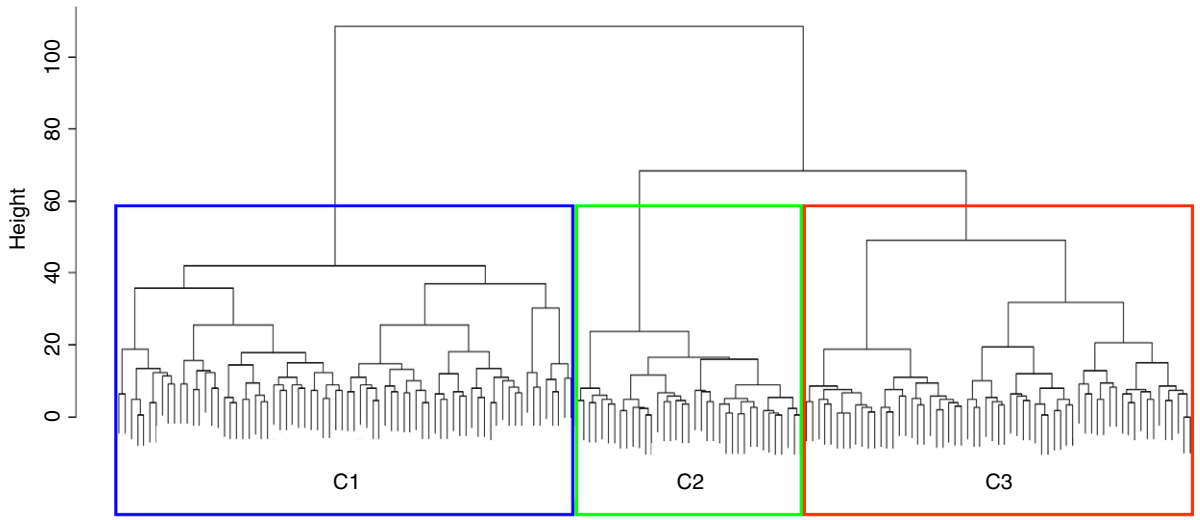


**Figure 1:** Cluster dendogram of hierarchical ascendant clustering of 174 children and adolescents with Tourette syndrome. C1, cluster 1; C2, cluster 2; C3, cluster 3. [Colour figure can be viewed at wileyonlinelibrary.com].

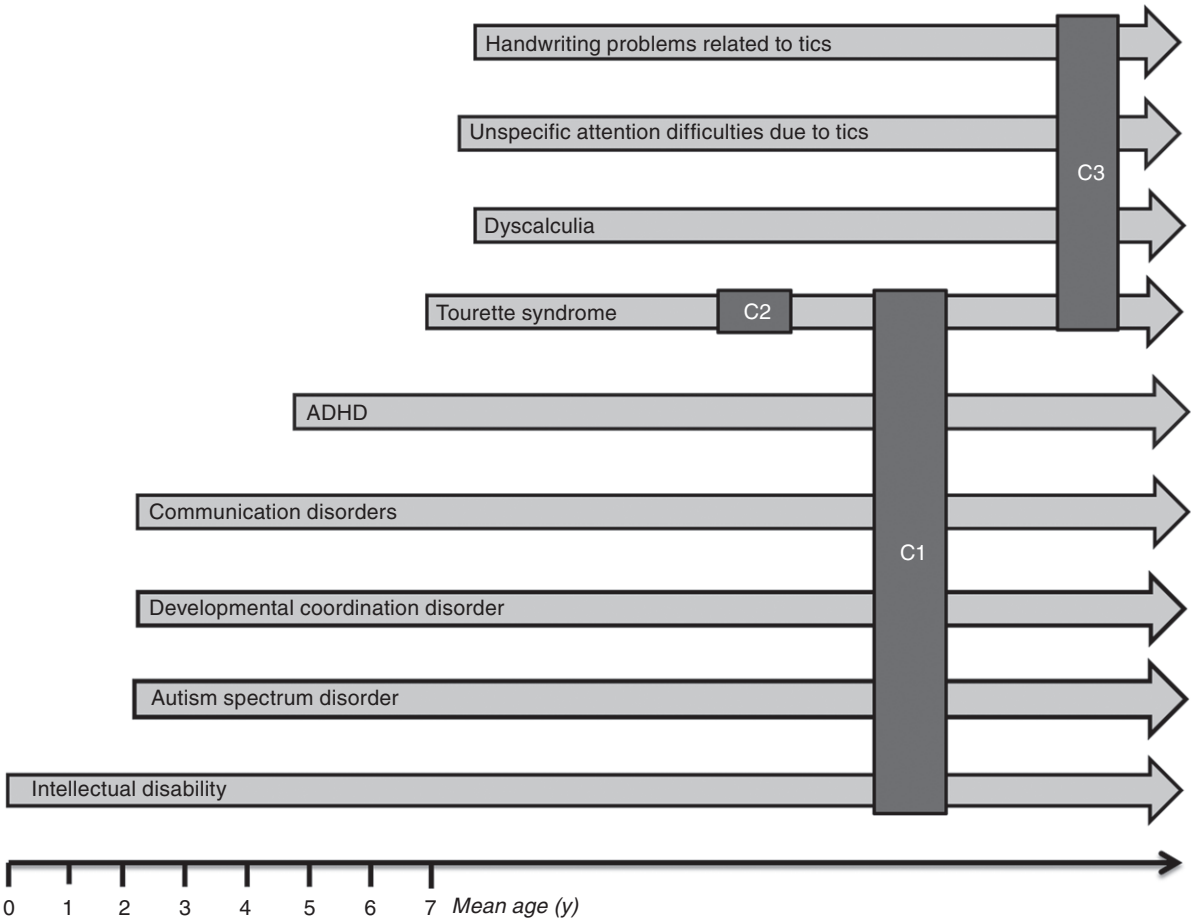


**Figure 2:** Clusters described in the sample according to the age at onset of comorbid neurodevelopmental disorders. C1, cluster 1; C2, cluster 2; C3, cluster 3; ADHD, attention-deficit–hyperactivity disorder.

occurring neurodevelopmental disorders necessitating a multidisciplinary therapeutic approach. In line with recent studies that correlated a more complex Tourette syndrome phenotype to a history of prenatal and perinatal complications,[26,27] we found higher rates of prenatal and perinatal risk factors in the cluster 1 group. The cluster 2 group was represented by 'pure' Tourette syndrome, thus including patients who showed only the core symptoms of the syndrome. The cluster 3 group, interestingly, was represented by a cluster less characterized by the current literature, including patients with the youngest age at first evaluation and presenting multiple school difficulties related not only to comorbidity with ADHD, but also to non-specific attention and writing problems secondary to the tics themselves. In agreement with many studies that did not find a correlation between tic severity and complexity of the Tourette syndrome phenotype,[28] we found that the clusters did not differentiate on the basis of tic severity as measured by the YGTSS.

### Comparison with previous studies

The approach adopted in our study is in line with recent works that highlight that Tourette syndrome is not a unitary condition and describes the complexity of the Tourette syndrome phenotype through data reduction and quantitative methods. Performing a sensible comparison of different studies requires a clear understanding of the different procedures and statistical methods utilized. It is important to answer the following questions. How was the sample of patients in the study recruited (bias of severity, of age)? What was the statistical approach to data reduction? What were the variables included in the data reduction? In previous studies (see Table SI), patients included were both children and adults recruited from specialized Tourette syndrome clinics or from samples collected for genetic studies. Studies using HAC[25,29] identified, so far, 2 to 4 clusters and used tic symptoms as variables to build the groups. Mathews et al.[29] analyzed two genetically isolated populations and identified two clusters: the first was represented by patients with predominantly simple tics and the second by those with multiple, complex tics. When comparing the two clusters on the basis of behavioural symptoms, cluster 2 was found to be correlated with the presence of comorbid obsessive-compulsive symptoms and ADHD. McGuire et al.[25] identified four clusters based on tic symptoms and found no associations with the presence of coexisting psychiatric conditions. Factor analysis of tic symptomatology has gathered from 2 to 5 factors.[3,4,30–34] The largest clinical cohort so far included 1191 patients with Tourette syndrome.[35] Using latent class analysis, the authors in this study found a three-class model: few OCD/ADHD symptoms; OCD and ADHD symptoms; and symmetry/exactness, hoarding, and ADHD symptoms. OCD and ADHD symptoms were found to have the highest psychiatry comorbidity rates, and ADHD was identified as an underlying vulnerability transcending diagnostic boundaries. Thus far, four studies[32,34–36] included the data reduction statistics with ADHD as a covariable, and only one adopted a 'neurodevelopmental perspective' including both ADHD and autism.[34] In this study, the authors reported a five-factor model: (1) tic, aggression, and symmetry; (2) obsessive-compulsive symptoms and compulsive tics; (3) ADHD symptoms; (4) autism symptoms; and (5) hoarding and inattention symptoms.

Our study is the first with a sample including only children and adolescents. This approach could contribute to better distinction between developmental, comorbid conditions that constitute a phenotype and transversal, coexistent disorders due to a chronic disease. In addition, after the Huisman-van Dijk et al.[34] study, this is the second study to include comorbid neurodevelopmental disorders as variables contributing to the development of the clusters. However, we extended the list of possible neurodevelopmental conditions through a two-step assessment process using specific tests leading us to include developmental coordination disorder, specific learning disorders, and communication disorders that are usually lacking in the literature.

The relevance of disaggregating Tourette syndrome into subgroups that are coherent in terms of clinical manifestations and course is related not only to a better comprehension of the etiopathogenesis but also to developing more comprehensive and patient-tailored therapeutic strategies. Additionally, the DSM-5 proposal of positioning Tourette syndrome within the neurodevelopmental condition group appears to be in line with the current data as anxious and depressive conditions including OCD were distributed equally across clusters. This finding is in line with recent literature demonstrating that Tourette syndrome likely shares a similar genetic background and risk factors with other conditions in this group that eventually produce similar neuropathological alterations. In particular, recent studies have noted that similar connectivity alterations found in ASD and ADHD are seen in patients with Tourette syndrome.[6]

### Limitations

The study results should be interpreted in the context of the study's limitations. First, the sample of patients includes only patients who were referred to a tertiary centre and therefore presented with a particularly severe form of Tourette syndrome. It is likely that this recruitment has resulted in selection bias as it can be inferred by the high rates of patients constituting the more complex cluster, and by the scores obtained on the YGTSS. Second, the two-step procedure we used to assess patients means that only a subgroup of patients received a detailed assessment in term of psychometric testing and speech and motor evaluation. In fact, the majority of patients were tested when a cognitive/language/motor deficit was suspected at step one. It also means that most variables were binary (present or absent), which limited the statistics that could be used. Third, when time was a component of a given variable, the time windows differed across variables

(e.g. 1wk before examination for tic severity vs early onset for ASD diagnosis). Only a prospective sample with repeated measures would allow proper statistics. Finally, another limitation of our study was the lack of description of genetic risk factors, but prenatal and perinatal events were investigated.

## CONCLUSION

In sum, our findings suggest that positioning Tourette syndrome in the DSM-5 neurodevelopmental disorder group seems to be particularly appropriate from a clinical point of view. The current study suggests that from a developmental perspective, Tourette syndrome is a heterogeneous syndrome with at least three main clusters defining a gradient of severity/complexity from simple Tourette syndrome to complex Tourette syndrome. For a more comprehensive phenotype definition, future studies should address the characterization of groups not only in terms of clinical manifestations but also in terms of neuropathological substrates through specific neuroimaging and genetic methods.


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## SUPPORTING INFORMATION

The following additional material may be found online:

**Figure S1:** Flow chart of the patients included in the Tourette syndrome sample.

**Table SI:** Overview of the data reduction quantitative methods applied to Tourette syndrome

**Table SII:** Socio-demographics, perinatal risk, family history, and clinical characteristics of all children and adolescents with Tourette syndrome

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