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Clinical features associated with an early onset in chronic tic disorders



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ABSTRACT

In chronic tic disorders such as Tourette syndrome (TS), tics often appear between 4 and 8 years but they can also appear in early childhood, a period in which symptom expression may be affected by early brain development. The present study examined whether symptom expression in early-onset TS was distinct from that observed in TS with a later onset. We compared the clinical characteristics in children with TS who developed tics before age 4 or after age 6. Early-onset TS was significantly associated with an increased rate of stuttering and other speech disfluencies as well as an increased rate of oppositional defiant disorder, symptoms that often appear before age 4. Early-onset TS was also linked to maternal transmission of tics. Early-onset TS was not significantly associated with tic severity, obsessive-compulsive behavior or attention-deficit hyperactivity disorder. The results suggest that an early onset affects symptom expression in tic disorders.

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1. Introduction

Gilles-de-la-Tourette syndrome (TS) is characterized by repetitive and stereotyped motor, and phonic tics which wax and wane in severity. The prevalence of TS remains unclear partly because of symptom fluctuations but it is estimated that about 1–2% of the school age population is affected by TS and 3–6% if chronic tic disorder (CT) (chronic motor tics or chronic phonic tics) are included as less severe phenotypes in the TS spectrum (Hornsey et al., 2001; Knight et al., 2012). In a majority of cases, TS is also associated with behavioral symptoms including obsessive-compulsive behavior (OCB), attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD) and temper outbursts (Stephens and Sandor, 1999; Cavanna et al., 2009; Bloch and Leckman, 2009; Grados and Mathews, 2009).

Tics generally appear during childhood with an average onset around 5 years, but tic onset can occur in the first years (Khalifa and Von Knorring, 2005; Bloch and Leckman, 2009). There is evidence that, on average, tic onset is earlier in severe TS than in less severe TS or in CT (Khalifa and Von Knorring, 2005). However, few studies have directly examined the characteristics associated

with an early onset of chronic tic disorders. The present study examined the possibility that tic disorders with an early onset could have a distinct clinical presentation. Such a distinct presentation could appear through interactions of the pathophysiology of tic disorders with early brain development or with other early neurodevelopmental conditions.

Early childhood is characterized by accelerated brain development. Critical steps in the development of neural circuits peak during the first post-natal years including neurite growth, synaptic proliferation, myelination and glial cell proliferation (Huttenlocher and Dabholkar, 1997; De Graaf-Peters and Hadders-Algra, 2006). This period has been linked to the pathophysiology of neurodevelopmental disorders such as autism (Courchesne et al., 2001; Dawson et al., 2007; Geschwind and Levitt, 2007). Early childhood is also characterized by a high level of functional plasticity and a rapid development of language and sensorimotor functions. Early-onset TS could be a more severe phenotype associated with increased severity of motor or phonic tics. It could also be linked to increased rates of comorbidities in particular ADHD, ODD and explosive outbursts which often appear at an early age. Early-onset TS could also interact with speech development and increase the rate of echolalia, palilalia or speech disfluencies such as stuttering which are often associated with early childhood. This study thus examined whether an onset of tics before age 4 affects symptom expression compared to a later onset of tics.

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2. Methods

2.1. Participants

The sample was composed of 131 children aged between 8 and 15 yrs ($M=10.9$ yrs, $SD=1.7$) taking part in a large genetic study on tic disorders. Participants were divided in two groups: an early onset group (onset of tics before 4 yrs old, $n=41$) and a later onset group (age of onset of tics between 6 and 8, $n=90$). As tic onset was obtained from parent recollections, patients with tic onset at age 4 and 5 were not considered to minimize the probability of group allocation errors. Groups were matched in age ($t(129)=1.35$, $p=0.18$) and sex ratio ($\chi^2(1)=0.14$, $p=0.71$).

All children were diagnosed by a neurologist or psychiatrist trained in tic disorders as definite or probable TS or chronic tic disorder (CT) as defined by the Tourette Syndrome Classification Study Group (Tourette Syndrome Classification Study Group, 1993). Tics were defined as brief, repetitive, non-rhythmic movements or sounds occurring individually or in bouts. Multiple motor tics and phonic tics (motor or phonic tics for CT) had to be present at some time during the illness, although not necessarily concurrently; tics had to occur many times a day, nearly every day, or intermittently throughout a period of more than one year; the anatomical location, number, frequency, type, complexity, or severity of tics had to change over time; the onset had to occur before the age of 21 years; involuntary movements and noises could not be explainable by other medical conditions; and tics had to be witnessed directly or from video by a reliable examiner (definite) or concluded from clinical history (probable).

Families were recruited at the Tourette clinic of Sainte-Justine hospital. Patients (above 14 yrs) or their parents gave written and informed consent to the research coordinator which was not involved in their care. The research was approved by the institutional review board. Exclusion criteria were: (a) inability to provide consent, (b) a history of head injury or other neurological disorder which may cause tics, (c) tics linked to drugs, (d) a psychotic disorder, (e) a history of pervasive developmental disorder or meeting DSM-IV criteria for autistic or Asperger's disorder, or (f) a history of abnormal movements besides tics including dystonia, chorea, paroxysmal movements, or rhythmic stereotypies.

2.2. Measures

Parents first filled out questionnaires on medical, obstetric, and developmental history for their children and for themselves. They also completed the Conners Parent Rating Scale (CPRS-L; Conners, 2003). A clinical evaluation followed consisting of multiple semi-structured interviews targeting specific symptom classes. Tics were evaluated using the Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989), and the worst lifetime severity of motor tics and phonic tics were used as the main measures. Young children may show motor stereotypies or other abnormal movements which may sometimes be mistaken for tics. However, only brief, non-rhythmic abnormal movements were counted as tics by evaluators. Motor tics most often involved blinks or movements of the face, head, arms, shoulders or legs.

Phonic tics were brief repetitive non-rhythmic sounds, including mouth noises, throat clearing, vocalizations, and screams. Echolalia, palilalia, and coprolalia were evaluated separately. Stuttering and other speech disfluencies were rated as present if they were clearly distinct from the phonic tics of an individual patient and could include speech initiation difficulties, speech prolongation, part-word repetitions and false starts (De Nil et al., 2005). Disfluencies are distinct from phonic tics in that tics occur independently of speech and patients suppress tics during speech. Disfluencies are also distinct from palilalia which involve festinating speech repetitions which gradually increase in rate and decrease in loudness.

OCB symptoms were evaluated through the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS; Goodman et al., 1989); ADHD and ODD were evaluated through a semi-structured interview using DSM-IV criteria (American Psychiatric Association, 2000). Interviews were conducted by trained professionals including neurologists, neuropsychologists and psychiatrists, and all had previous experience with patients with tic disorders and their evaluation. During interviews, professionals reviewed the questionnaires with the parents to ensure clarity and correspondence with the information shared during interviews and also to obtain a consensus between parents on the child's symptom history.

3. Results

Table 1 summarizes clinical and demographic data on the patients. Groups were compared using *t*-tests for continuous variables or chi-square tests for categorical variables. The proportion of patients with only motor or phonic tics (CT) was not significantly different in the two groups (early-onset: 9.9%, later-onset: 5.5%, $\chi^2(1)=0.7$, $p=0.38$). The two groups were not significantly different on the worst severity of motor tics ($t(127)=1.7$,

Table 1

Demographic and clinical data on patients in the early-onset and late-onset groups (Standard deviations are in parentheses).

	Early onset	Late onset
N	41	90
Age at evaluation (yrs)	9.6 (2.6)	11.3 (1.9)
% males	84.5	82.3
Worst motor tic severity	3.6 (1.2)	3.3 (1.2)
Worst phonic tic severity	3.3 (1.5)	2.6 (1.4)
% Echolalia	39	31
% Palilalia	10	13
% Coprolalia	24	17
% Speech disfluencies	20*	3
YBOCS score	12.1 (9.1)	10.9 (8.8)
% ADHD	69	58
% ODD	65*	48
% Explosive outbursts	66	56

* $p < 0.05$.

$p=0.09$) or phonic tics ($t(94)=1.4$, $p=0.18$). Also, the two groups were not significantly different on the rates of echolalia ($\chi^2(1)=0.4$, $p=0.53$), palilalia ($\chi^2(1)=0.3$, $p=0.56$), and coprolalia ($\chi^2(1)=1.1$, $p=0.30$). However, the early-onset group showed a significantly higher rate of stuttering or other speech disfluencies ($\chi^2(1)=9.6$, $p=0.002$, $r=0.24$).

As for behavioral co-morbidities, the two groups were also significantly different on the rate of ODD ($\chi^2(1)=4.9$, $p=0.02$, $r=0.2$), but not on the rate of ADHD ($\chi^2(1)=2.5$, $p=0.2$), on the rate of explosive outbursts ($\chi^2(1)=0.94$, $p=0.33$), or on YBOCS scores ($t(117)=0.11$, $p=0.91$).

We also examined whether the two groups differed in terms of parental symptoms. The presence of tics in one of the parents was not significantly different in the two groups ($\chi^2(1)=0.4$, $p=0.52$). However, early tic onset was significantly more associated with maternal transmission than paternal transmission when tics were present in parents ($\chi^2(1)=5.1$, $p=0.02$, $r=0.25$). None of the other parental symptoms were significantly associated with age of onset of tics in children.

4. Discussion

The present results suggest that an early onset of tic disorders is associated with increased rates of speech disfluencies and oppositional defiant disorder.

The age of onset measure used for group assignment was dependent on parent recollections. The exclusion of children with an age of onset between 4 and 6 years (the most common ages of onset of tics) was designed to minimize errors in group membership. However, group assignment may have been affected by symptom expression since severe symptoms can be noticed earlier than less severe symptoms. If the patients in the later onset group showed tics before age four without the parents noticing them, this could have led to an underestimation of group differences. This, however, cannot explain the significant differences observed. Abnormal movements other than tics can be observed in toddlers including stereotypies and dystonia but children with these movements were excluded in the present study.

The high prevalence of speech disfluencies in early-onset TS is interesting because of the temporal overlap between the predominant onset period of speech disfluencies (age 2–4) and early tic onset as defined here. Developmental stuttering usually involves speech initiation difficulty including part-word and single syllable word repetitions as well as speech prolongation (Yairi and Ambrose, 2013). However, many young children show normal developmental disfluencies which are not considered specific to

developmental stuttering including hesitations and false starts (De Nil et al., 2005; Van Borsel and Tetnowski, 2007). In the present study, stuttering and other disfluencies could not be reliably differentiated from each other from parental reports and were thus considered together. Disfluencies are distinct from phonic tics in that tics can occur independently of speech. Disfluencies are also distinct from palilalia which involve festinating speech repetitions which gradually increase in rate and decrease in loudness.

There is evidence for high rates of tics in persons with developmental stuttering (Abwender et al., 1998; Mulligan et al., 2003). There is also evidence of a higher prevalence of stuttering in children with TS compared to non-TS samples (Leckman et al., 1999). However, it is still unclear if this association is linked to a higher prevalence of normal developmental disfluencies in TS or to a higher prevalence of developmental stuttering specifically (De Nil et al., 2005). Our data suggest that the higher prevalence of speech disfluencies in TS may be more specifically linked to patients with early-onset TS.

The association between dysfluencies and early tic onset may be due to the fact that the presence of one symptom exacerbates the other through increased stress. Both stuttering and tics can be stigmatizing and thus may contribute to increased anxiety which in turn may amplify all sub-clinical motor symptoms. Another possibility is that the two motor control problems may share portions of their pathogenesis. There is evidence of a dysregulation of basal ganglia in developmental stuttering (Craig-McQuaide et al., 2014) as well as in tic disorders (Makki et al., 2008; Müller-Vahl et al., 2014). It has been suggested that developmental stuttering is linked to an abnormal activity-dependent refinement of neural networks during early childhood (Ludlow and Loucks, 2003). This hypothesis may also apply to early-onset TS. Prospective studies of speech in children at risk for TS should help clarify the developmental trajectories of both early tics and speech disfluencies. This may help clarify a number of questions on developmental stuttering, such as the possible role of tics in the persistence of stuttering especially in boys (Yairi and Ambrose, 2013).

Early tic onset was also associated with an increased rate of ODD but not of other behavioral comorbidities. Like stuttering, ODD often starts before the age of 4 (Keenan et al., 1998). The association between ODD and early-onset TS may be due to an exacerbation of ODD symptoms by stress linked to tics in early childhood. On the other hand, emotional dysregulation is known to exacerbate tics, so it is also possible that ODD symptoms could facilitate the early appearance of tics in individuals at risk for the development of TS. A third possibility is that early TS and ODD may interact through portions of their pathogenesis. None of these possibilities can be ruled out with the present data. Clinically, our data suggest that special attention should be given to children with early chronic tics to increase stress resilience and reduce tic-related emotional reactions.

Early-onset TS was not significantly associated with an increased rate of ADHD. This is surprising given that ADHD also often has an early onset and is often associated with ODD. This lack of association may be linked to characteristics of our sample which, as in many clinical samples, included a high proportion of children with ADHD because it is one of the main reasons for clinical consultation.

Early tic onset was also associated with maternal transmission of tics. This result confirms a previous report of an earlier onset of tics in patients with a maternal transmission of tics (Pauls et al., 1981; Eapen et al., 1997). One possible explanation for this association is that mothers with tic disorders may be more sensitive to their children's symptoms than unaffected mothers, which would affect symptom recall differentially in the two groups. Another possibility is that prenatal or perinatal environmental factors

including maternal stress, growth retardation, or contaminant exposures which affect tic severity (Motlagh et al., 2010; Hoekstra et al., 2013) may also affect tic onset and may be more prevalent in maternally transmitted cases. A third possible explanation is a maternally transmitted epigenetic modification or genomic imprinting which may be linked to tic onset. These possibilities should be examined in future studies.

Previous evidence has suggested that an increased severity of TS is associated with an earlier onset of tics (Spencer et al., 1995; Khalifa and Von Knorring, 2005; Scharf et al., 2012). We could not confirm this in our group comparisons, possibly because of the small size of the early-onset group which may have lowered statistical power. When we examined a larger cohort of 238 patients aged 8–15 with tic onset between 0 and 13 years, we found a small but significant association between an earlier age of onset of tics and higher tic severity on ($r=0.125$, $p=0.05$). However, we found little evidence to support that when TS appears in toddlers, this will lead to a significantly more severe phenotype.

The interpretation of the present data is limited by a number of factors. Firstly, as mentioned, symptom severity can affect parental reports of symptoms and the relationships observed here will have to be confirmed in prospective studies. Also, our sample is a clinical sample from a specialized TS clinic. Community samples generally show a lower severity for many symptoms and the observed links between early-onset and symptom profile may differ in community samples. Also, we did not investigate the link between early tic onset and autism spectrum disorder (ASD). Children with a clear autistic disorder or stereotypies were excluded but ASD symptoms may have been present in our sample. ASD is present in more than 10% of children with chronic tic disorders and is also an early onset neurodevelopmental disorder which can present with many symptoms that overlap those seen in TS including tics, echolalia, ADHD, OCB, and stuttering. Prospective studies on the links between early-onset TS and ASD may help elucidate some of the pathways for the overlap between TS and ASD. Finally, causal links cannot be ascertained from cross-sectional correlation data. To determine if developmental trajectories differ in patients with early TS compared to patients with a later onset, children at risk of developing chronic tic disorders should be evaluated longitudinally.

In conclusion, our data suggest that an early onset of tics in TS is associated with a distinct clinical presentation, including a higher rate of speech disfluencies and of oppositional defiant disorder.

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