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Research report

Admixture analysis of age at symptom onset and age at disorder onset in a large sample of patients with obsessive–compulsive disorder

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ABSTRACT

Background: A number of studies tested for the presence of different homogeneous subgroups of obsessive–compulsive disorder (OCD) patients depending on the age at onset (AAO). However, none of the various thresholds of AAO have been validated. No study examined whether age at symptoms onset (ASO) and age at disorder onset (ADO) each define specific and diverse OCD subgroups.
Methods: We used normal distribution mixture analysis in a sample of 483 OCD patients to test whether we could identify subgroups of patients according to the AAO. We tested whether ASO and ADO had different distributions and identified different subgroups of OCD patients, and whether clinical correlates had similar patterns of associations with patients subgroups identified with ASO or ADO.
Results: The mixture analysis showed a trimodal distribution for ASO (mean ASO: 6.9 years for the early onset, 14.99 years for the intermediate onset, and 27.7 years for the late onset component), and confirmed a bimodal distribution for ADO (mean ADO: 18.0 and 29.5 years). Significant differences in the clinical profile of the subgroups emerged, particularly when identified using ASO.
Limitations: Limitations of our study are the retrospective investigation of AAO, and the fact that our sample may not represent the OCD population, as we enrolled patients referring to a tertiary center specialized in the treatment of OCD. Our findings need to be confirmed in community samples. Another limitation is the lack of information on medication status at enrollment.
Conclusions: Age at symptom onset and ADO showed distinct patterns of distributions. Similarly, phenotypic delineation was specific for ASO and ADO identified subgroups. Accurate clinical and biological profiling of ADO and ASO subgroups might show distinct genetic liabilities, ultimately leading to better nosological models and possibly to improved treatment decision making of OCD patients.

1. Introduction

Obsessive–compulsive disorder (OCD) is a complex psychiatric disorder with a multifactorial etiology. Biopsychosocial factors, including environmental and genetic factors play a key role in modulating the liability to OCD (Taylor et al., 2010). Indeed, OCD is familial and appears to be heritable: the risk for OCD in relatives is proportionally higher with increasing genetic relatedness to the proband (Mataix-Cols et al., 2013). Furthermore, up to 10% of OCD patients referred for treatment have at least another family member affected by the same disorder (Albert et al., 2002b). Despite this evidence, little is known about the genetic architecture of OCD: molecular association studies have as yet yielded inconsistent results. Multiple genes appear to each confer a small contribution to the risk of developing OCD, suggesting a polygenic model of liability (Browne et al., 2014). These molecular genetic findings are consistent with early twin studies of the disorder (Taylor, 2013).

The search for genetic determinants of OCD has been hindered by its relatively high clinical heterogeneity. Thus, genetic analyses may take advantage from strategies aimed at reducing the phenotypic variability of OCD such as the investigation of moderator variables as, for instance, those defined by age at onset (AAO) (Taylor, 2013). Several such subtypes or dimensional specifiers have been proposed (Leckman et al., 2010), but to date only the degree of insight and the presence of a lifetime diagnosis of tic

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disorder were considered to have sufficient reliable evidence to be considered clinically informative and were accepted in the DSM-5.

A number of studies tested for the presence of different homogeneous subgroups of OCD patients depending on the AAO. Results were contradictory mainly because different and arbitrary cut-off points between early onset (EO) and late onset (LO) subgroups were applied in each study (Albert et al., 2002c; Bellodi et al., 1992; Chabane et al., 2005; Grant et al., 2007; Janowitz et al., 2009; Maina et al., 2008; Pauls et al., 1995). Moreover, no consensus has been reached concerning the best discriminative AAO, given that some studies used age at symptoms onset (ASO) (Butwicka and Gmitrowicz, 2010; de Mathis et al., 2009), while others employed age at disorder onset (ADO) (i.e. when symptoms reached a clinically significant intensity and impaired patient functioning, or when full diagnostic criteria were met) (Maina et al., 2008; Taylor, 2011; Tukel et al., 2005). To date, none of the various thresholds of AAO have been validated, so that a distinction in subgroups differing in clinical characteristics, prognosis and therapeutic response based on AAO is not considered in the current classification system. Indeed, the OCD Working Group for DSM-5 took the decision not to recommend AAO as clinical classifier of OCD subtypes and as a result DSM-5 only lists the insight and tic specifiers /subgroups.

Admixture analysis of AAO has been used to reduce the clinical heterogeneity, and possibly the genetic and neurobiological one, of different psychiatric illnesses such as bipolar disorder, major depressive disorder, panic disorder, social phobia, and schizophrenia (Aderka et al., 2012; Azorin et al., 2013; Liu et al., 2013; Manchia et al., 2008; Ortiz et al., 2011; Tibi et al., 2013; Tozzi et al., 2011; Zhu et al., 2012). Only three studies, to date, used admixture analysis to test whether different subpopulations of OCD patients could be identified according to the AAO (Anholt et al., 2014; Delorme et al., 2005). They used retrospectively assessed ADO and were concordant in showing a bimodal distribution of AAO. Clinical differences emerged between EO and LO OCD subgroups, suggesting the potential utility of AAO in isolating more homogeneous and clinically informative illness subtypes. The clinical characteristics of the subgroups, however, differed between the three studies, suggesting the need of more research in different and greater samples. In addition, no study examined the hypothesis that ASO and ADO might each define specific and diverse OCD patients' subgroups. Since the threshold of symptomatological severity for OCD onset is conventionally established (for instance in DSM-5 OC symptoms should cause distress or should be time consuming, e.g. take more than 1 h per day), the investigation of the clinical features associated with specific onset subgroups may result in a better nosological model and be more informative. Indeed, the identification of reliable and homogeneous illness subgroups is the prerequisite for studies investigating the biological and genetic basis of psychiatric disorders.

The main aim of the present study was to test: (1) whether ASO and ADO had different distributions and identified different subgroups of OCD patients; (2) whether clinical correlates had similar patterns of associations with patients subgroups identified with ASO or ADO; (3) replicate and extend previous findings of admixture analysis of ADO in OCD. Thus, we performed two separate admixture analyses on ASO and ADO to test which model could be more informative in identifying homogeneous and clinically different subgroups. We also added to the existing literature by analyzing several different socio-demographic and clinical variables in a large sample of well-characterized OCD patients.

2. Methods

2.1. Subjects

Our sample consisted of 483 unrelated patients with OCD. All subjects were of Italian ancestry. Participants were recruited consecutively among subjects referred to the Psychiatric Section of the Department of Neuroscience, University of Turin (Italy); this is a tertiary referral center located within the University Hospital and specialized in the treatment of patients with OCD. After a detailed description of the study procedures, informed written consent to participate in the study was obtained from all patients. The local Ethical Committee approved the study. To be enrolled in the study, patients fulfilled the following inclusion criteria: (a) a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) principal diagnosis of OCD according to the Structured Clinical Interview for Axis I Disorders (SCID-I/P); (b) at least 18 years of age; (c) a minimum total score of 16 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989a, b). (d) OCD duration exceeding 1 year.

2.2. Assessments and procedures

Data were obtained from each patient by a semi-structured interview that we developed and used in previous studies (Albert et al., 2002a, 2013; Bogetto et al., 1999; D'Ambrosio et al., 2010; Maina et al., 1999) with a format that covered the following areas: (a) socio-demographic data (age, gender, marital status, years of education and occupational status); (b) diagnosis: diagnoses (current and lifetime) were performed by clinicians with at least four years of postgraduate clinical experience by means of the Structured Clinical Interview for DSM Axis I Disorders (SCID-I); (c) clinical data (AAO, type of onset, duration of illness, course of the disorder). In addition, the following rating scales were included in the assessment: Y-BOCS, including the Y-BOCS Symptoms Check List; 17-item Hamilton Depression Rating Scale (HAM-D); Hamilton Anxiety Rating Scale (HAM-A); and the Clinical Global Impression Scale-Severity of Illness (CGI-S). All assessments were conducted in Italian, with the Italian versions of the SCID-I (Mazzi et al., 2000) and of the rating scales (Y-BOCS, HAM-D, HAM-A, CGI-S) (Conti, 1999).

Age at symptoms onset was defined as the age at which subjects first presented OCD symptoms. Age at diagnosis onset was defined as the first reliably diagnosed OCD episode according to DSM-IV diagnostic criteria, using all the available medical records. Illness duration was calculated subtracting ADO from age. External corroboration for AAO was obtained, whenever possible, by directly interviewing, with patient's consent, a first-degree family member or other significant individuals. For the purposes of the present study, we included only subjects for whom it was possible to establish the onset of symptoms and that of disorder with complete agreement between the information provided by patients and their relatives. An attempt was made to date the onset of symptoms and of OCD in a 4-week period; if there was uncertainty, a range was plotted and its mid-point was used for the analysis. The onset was considered abrupt when the symptoms reached clinically significant intensity within 1 week of onset. All other types of onset were considered insidious. The interval between the onset of symptoms and the onset of OCD was recorded. The course of the disorder was considered episodic when at least one circumscribed symptom-free interval (6 months) was present; all other types of course were considered chronic, according to a definition we used in previous studies (Ravizza et al., 1995, 1997).