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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.

Keywords: Obsessive–compulsive disorder; Age at onset; Admixture analysis; Early onset.

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 disorderwere 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 and 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 and 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 and 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 and 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 and 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., 1989b and Goodman et al., 1989a). (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, Albert et al., 2013, Bogetto et al., 1999, D'Ambrosio et al., 2010 and 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 and Ravizza et al., 1997).

2.3. Statistical analyses

We used normal distribution mixture analysis to test whether we could identify subgroups of patients according to the AAO. We investigated a range of number of AAO groups (1–9). The choice of the mixture model that best fit the distribution of AAO was made according to the Schwarz's Bayesian information criteria (BIC). Specifically, the analysis performed with the "Mclust" (Fraley and Raftery, 1999 and Fraley et al., 2014) package implemented in R (R Development Core Team., 2008) indicates the best model as the one with the highest BIC among the fitted models (Fraley and Raftery, 2007). Cut off points were derived using the theoretical ASO or ADO function and calculating each data point's probability of belonging to each class. The mixture analysis was also replicated and confirmed with the "Mixtools" R package (Benaglia et al., 2009). Further, a sensitivity analysis of admixture modeling was performed on subsamples of patients whose average ADO was similar to that of previously published studies. We used Kolmogorov–Smirnov (K–S) test to determine whether the theoretical ASO function was significantly different from the one identified for ADO.

We tested the association of continuous and categorical clinical variables with ASO and ADO subgroups using univariate analysis (t-test or contingency tables as appropriate). Non-parametric tests were used when data violated the assumption of normality. The independent variables tested included categorical [gender, employment status, presence of family history of OCD, presence of family history of mood disorders, presence of family history of anxiety disorders, mode of onset, type of clinical course, current comorbidity with a psychiatric disorder, lifetime comorbidity with a psychiatric disorder, current comorbidity with mood disorders, lifetime comorbidity with mood disorders, current comorbidity with anxiety disorders, lifetime comorbidity with anxiety disorders, comorbidity with tic disorder, presence of personality disorders, presence of cluster A personality disorders, presence of cluster B personality disorders, presence of cluster C personality disorders, and the following items of the Y-BOCS categorized as dichotomous variables (presence/absence): aggressive obsessions, contamination obsessions, sexual obsessions, hoarding/saving obsessions, religious obsessions, obsessions with need for symmetry or exactness, somatic obsessions, cleaning/washing compulsions, checking compulsions, repeating compulsions, counting compulsions, ordering/arranging compulsions, hoarding/collecting compulsions], and continuous ones (age, years of education, Y-BOCS total score, Y-BOCS obsessions total score, Y-BOCS compulsions total score, Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale). We used a more stringent $p=0.01$ as a threshold for statistical significance to decrease the risk of Type I error. And in order not to overly inflate the risk of Type II errorwe reported results with $0.01<p<0.05$ as trend associations. We entered the variables associated at both significant thresholds into a multinomial logistic regression model to account for intercorrelations. As OCD symptoms severity can manifest with higher severity at later stages of the clinical course, we included illness duration into the logistic model.

3. Results

3.1. Mixture analysis and comparison of ASO and ADO distributions

Our sample of 483 OCD patients (251 males and 232 females) had a mean age of 34.4 years (SD=12.2). The mean ASO and ADO were 17.1 years (SD=8.7) and 22.1 years (SD=9.1). The mixture analysis on ASO showed a best fitting theoretical model of three normal components (BIC: −3348.3) (Fig. 1). Models with two and four components did not improve the fit (Table 1). The mean ASO was 6.9 years (SD=1.13) for the EO component, 14.99 years (SD=4.21) for the intermediate onset (IO) component, and 27.7 years (SD=9.56) for the LO, with 12.4%, 63.5% and 24.1% of the population proportion, respectively. We obtained two cut-off points at 9 and 24 years dividing the sample into three subgroups: the EO (ASO≤9), the IO group (10≤ASO≤23), and the LO subgroup (ASO≥24 years). Eight-six patients were included in the EO subgroup, 309 in the IO subgroup, and 88 in the LO subgroup.

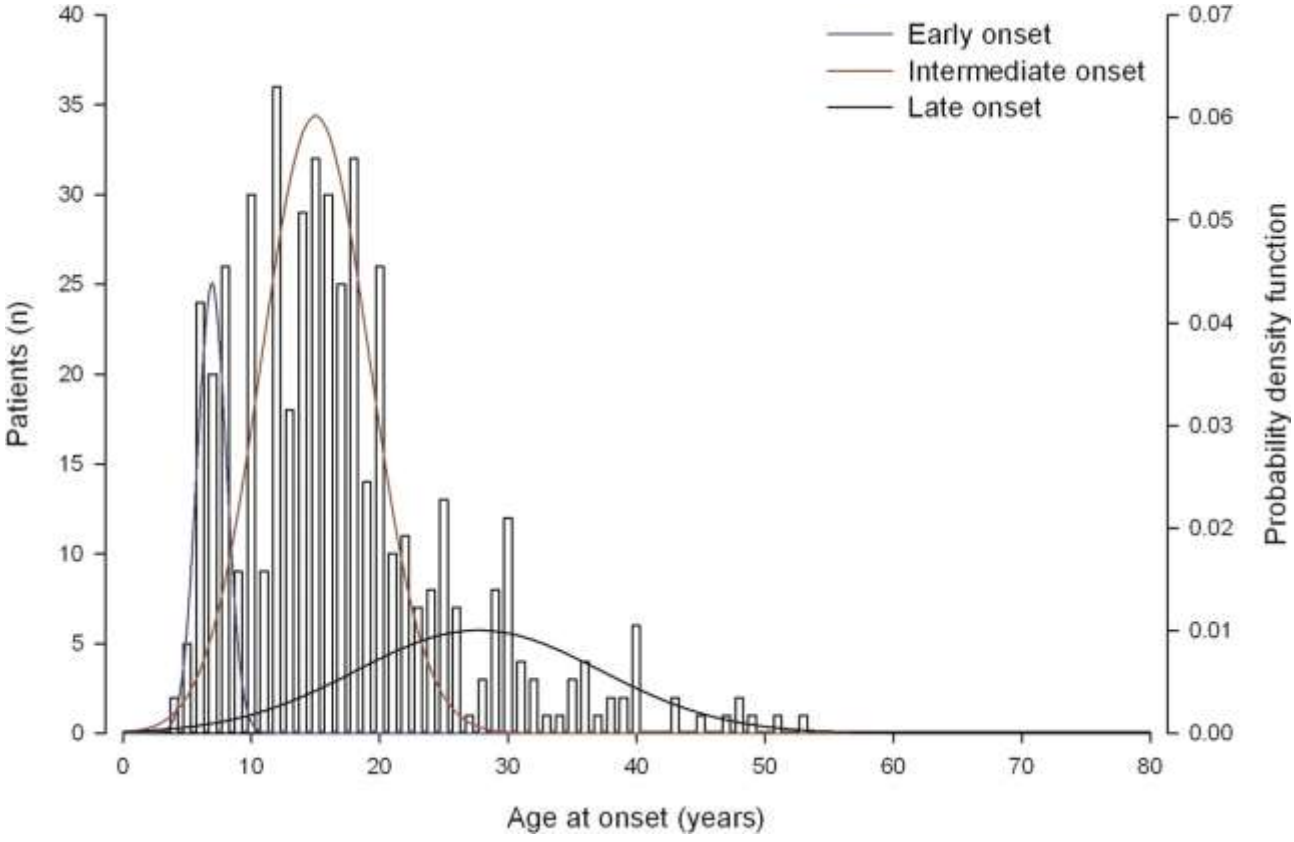

Fig. 1. Observed and theoretical distributions of age at symptom onset (ASO) in OCD (N=483).

Table 1. Age at symptoms onset and age at diagnosis onset distributions identified by mixture analysis in 483 obsessive compulsive disorder patients.

Age at symptom onset distribution (*N*=483)					
Mixture model	BIC	Model components	Mean	SD	Proportion (%)
M1	−3475.5	1st component	17.0	8.7	100.0
M2	−3368.8	1st component	13.7	4.9	75.0
		2nd component	27.0	9.9	25.0
M3	−3348.3	1st component	6.9	1.1	12.4
		2nd component	15.0	4.2	63.5
		3rd component	27.7	9.6	24.1
M4	−3365.6	1st component	6.8	1.1	12.9
		2nd component	12.4	2.9	31.7
		3rd component	17.7	3.1	30.1
		4th component	27.3	9.6	25.3
Age at diagnosis onset distribution (N=483)					
Mixture model	BIC	Model components	Mean	SD	Proportion (%)
M1	−3510.9	1st component	22.1	9.1	100.0
M2	−3400.3	1st component	18.0	4.5	64.0
		2nd component	29.5	10.3	36.0
M3	−3403.6	1st component	16.8	2.1	22.0
		2nd component	19.7	6.1	54.5
		3rd component	32.6	10.4	23.5
M4	−3418.5	1st component	14.0	4.0	20.0
		2nd component	17.3	2.2	30.6
		3rd component	24.2	3.9	27.0
		4th component	33.5	10.1	22.4

The observed distribution of ADO was best fitted by two normal components models (BIC=−3400.3) (Fig. 2). Models with three and four components did not improve the fit (Table 1). Specifically, the mixture normal model had an EO component with mean 18.0 years (SD=4.5) and a LO component with mean 29.5 years (SD=10.3) with 64.0% and 36.0% of the population proportion, respectively. The cut-off point was at 26 years dividing the sample in two subgroups: the EO (ADO≤26), and the LO subgroup (ADO>26). Three hundred and sixty nine patients were included in the EO subgroup, while 114 were in the LO. The sensitivity analysis of admixture modeling confirmed a trimodal and bimodal best fitting models for ASO and ADO, respectively (data not shown).

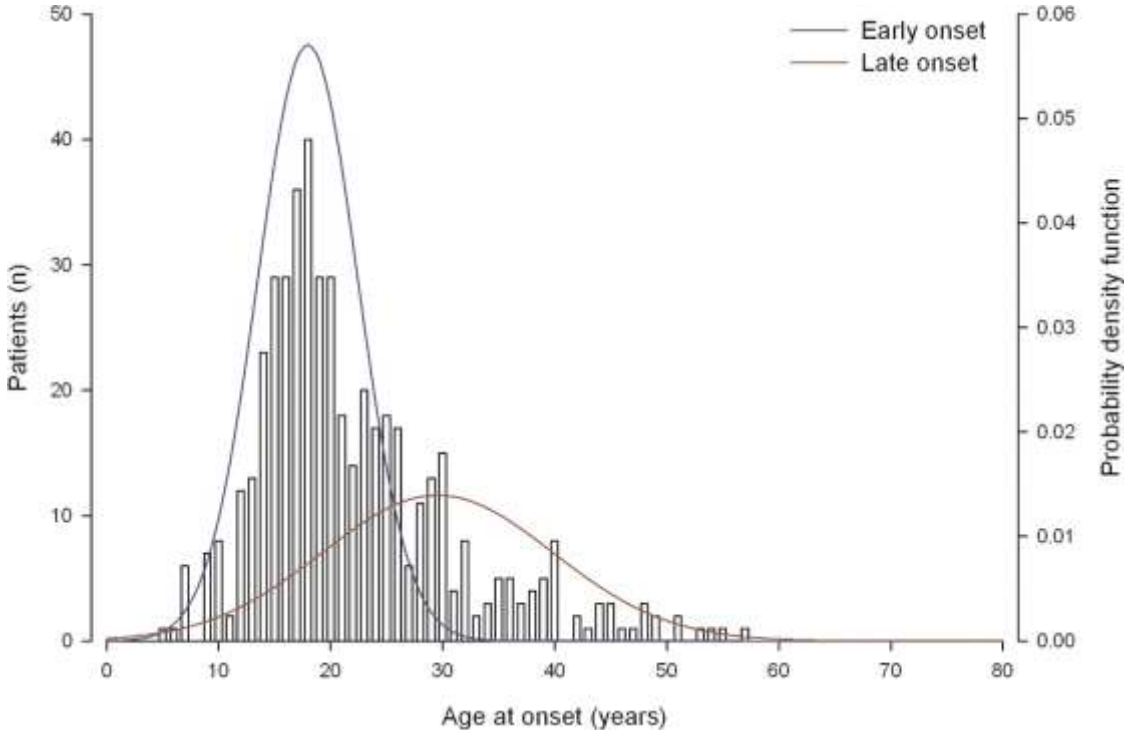

Fig. 2. Observed and theoretical distributions of age at disorder onset (ADO) in OCD (*N*=483).

Applying Kolmogorov–Smirnov (K–S) test, we found that the theoretical ASO function differed significantly from that of ADO (D=0.3, p<0.00001) (Fig. 3).

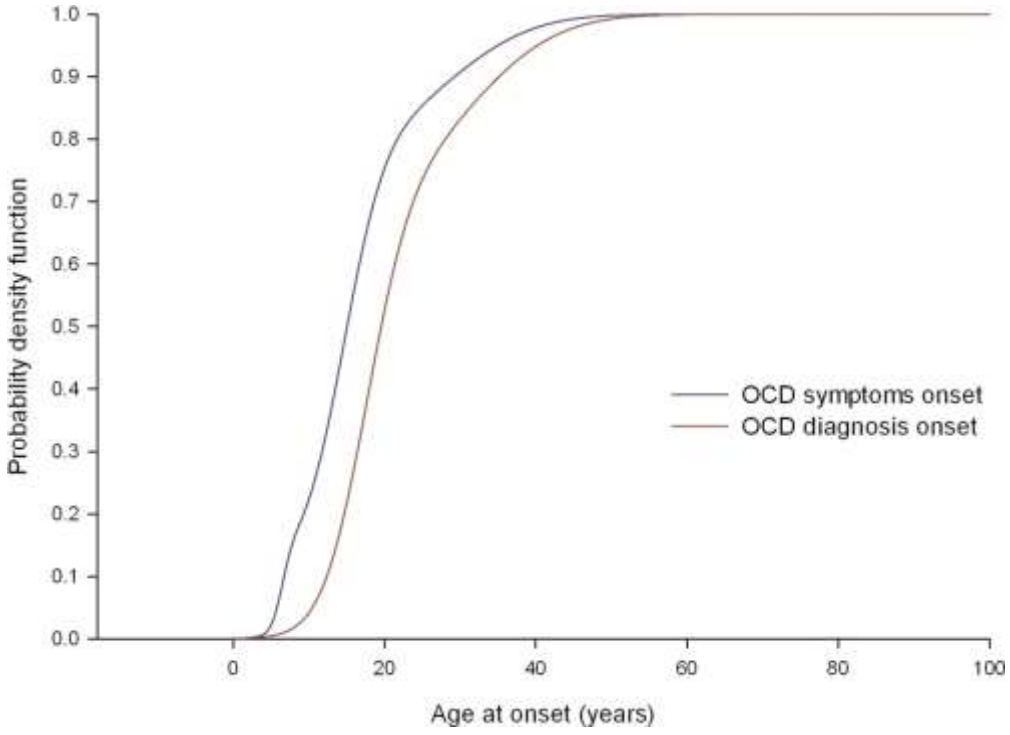

Fig. 3. Symptom onset versus disorder onset.

3.2. Clinical correlates of early ASO and ADO

As shown in Table 2, early and intermediate ASO patients were more likely to have an insidious mode of onset of OCD, as well as a more chronic clinical course compared to late ASO subjects. Similarly, the early ASO subgroup was also characterized by a higher rate of religious, cleaning/washing obsessions, as well as a higher rate of obsessions with need for symmetry or exactness. Early ASO patients had also a higher rate of cleaning/washing, repeating and counting compulsions. Early and intermediate ASO patients were also significantly younger, and presented a higher severity of OCD symptoms as shown by a higher mean of the total Y-BOCS compulsion scale score. Finally, the mean Y-BOCS total score and the rate of hoarding/collecting compulsions were marginally significantly higher in early ASO patients, while the mean HARS score was marginally significantly higher in the late ASO subgroup.

Table 2. Comparison of clinical correlates between age at symptoms onset subgroups in 483 obsessive compulsive disorder patients.

Clinical variable	**Early age at symptoms onset (*N*=86)**	**Intermediate age at symptoms onset (*N*=309)**	**Late age at symptoms onset (*N*=88)**	***χ2* or *F***	***p***
Female, % (N)	44.2 (38)	46.3 (143)	58.0 (51)	4.3	0.1
Employment status, % (N)	40.7 (35)	43.7 (135)	55.7 (49)	4.9	0.09
Presence of family history of OCD, % (N)	24.4 (21)	19.1 (59)	19.3 (17)	1.3	0.5
Presence of family history of mood disorders, % (N)	37.2 (32)	30.4 (94)	31.8 (28)	1.4	0.5
Presence of family history of anxiety disorders, % (N)	12.8 (11)	12.3 (38)	10.2 (9)	0.3	0.8
Mode of onset					
Abrupt,% (N)	12.8 (11)	27.2 (84)	52.3 (46)	34.5	<0.0
Insidious, % (N)	87.2 (75)	72.8 (225)	47.7 (42)		001
Type of clinical course					
Episodic, % (N)	9.3 (8)	14.9 (46)	28.4 (25)	13.0	0.002
Chronic, % (N)	90.7 (78)	85.1 (263)	71.6 (63)		
Current comorbidity with a psychiatric disorder, % (N)	67.4 (58)	70.2 (217)	69.3 (61)	0.3	0.9
Lifetime comorbidity with a psychiatric disorder, % (N)	77.9 (67)	79.0 (244)	79.5 (70)	0.07	1.0
Current comorbidity with mood disorders, % (N)	48.8 (42)	55.0 (170)	61.4 (54)	2.8	0.25
Lifetime comorbidity with mood disorders, % (N)	61.6 (53)	61.8 (191)	68.2 (60)	1.3	0.5
Current comorbidity with anxiety disorders, % (N)	14.0 (12)	18.8 (58)	22.7 (20)	2.2	0.3
Lifetime comorbidity with anxiety disorders, % (N)	19.8 (17)	25.9 (80)	29.5 (26)	2.3	0.3
Comorbidity with tic disorder, % (N)	11.6 (10)	7.1 (22)	4.5 (4)	3.3	0.2
Personality disorders, % (N)	56.8 (42)	55.0 (143)	47.1 (32)	1.6	0.4
Cluster A, % (N)	12.2 (9)	14.2 (37)	8.8 (6)	1.4	0.5
Cluster B, % (N)	14.9 (11)	18.8 (49)	11.8 (8)	2.2	0.3
Cluster C, % (N)	36.5 (27)	36.2 (94)	30.9 (21)	0.7	0.7

Clinical variable	Early age at symptoms onset (*N*=86)	Intermediate age at symptoms onset (*N*=309)	Late age at symptoms onset (*N*=88)	$\chi 2$ or *F*	*p*
Y-BOCS-Aggressive obsessions, % (N)	63.5 (54)	54.2 (166)	58.1 (50)	2.4	0.3
Y-BOCS-Contamination obsessions, % (N)	60.0 (51)	52.3 (160)	46.5 (40)	3.2	0.2
Y-BOCS-Sexual obsessions, % (N)	30.6 (26)	20.6 (63)	15.1 (13)	6.4	0.04
Y-BOCS-Hoarding/Saving obsessions, % (N)	21.2 (18)	17.0 (52)	9.3 (8)	4.7	0.1
Y-BOCS-Religious obsessions, % (N)	45.9 (39)	18.9 (55)	16.3 (14)	32.0	<0.001
Y-BOCS-Obsessions with need for symmetry or exactness, % (N)	61.2 (52)	49.3 (151)	32.6 (28)	14.3	0.001
Y-BOCS-Somatic obsessions, % (N)	32.9 (28)	30.4 (93)	26.7 (23)	0.8	0.7
Y-BOCS-Cleaning/Washing compulsions, % (N)	70.6 (60)	52.9 (162)	50.0 (43)	9.7	0.008
Y-BOCS-Checking compulsions, % (N)	75.3 (64)	65.0 (199)	70.9 (61)	3.6	0.2
Y-BOCS-Repeating compulsions, % (N)	67.1 (57)	51.3 (157)	39.5 (34)	13.1	0.001
Y-BOCS-Counting compulsions, % (N)	32.9 (28)	19.9 (61)	10.5 (9)	13.4	0.001
Y-BOCS-Ordering/Arranging compulsions, % (N)	37.6 (32)	28.1 (86)	23.3 (20)	4.6	0.1
Y-BOCS-Hoarding/Collecting compulsions, % (N)	23.5 (20)	14.1 (43)	9.3 (8)	7.3	0.03
Age, mean (SD)	30.7 (11.5)	33.4 (11.8)	41.6 (11.1)	21.9	<0.001
Years of education, mean (SD)	12.8 (3.0)	12.5 (4.2)	11.8 (4.0)	1.4	0.2
Y-BOCS total score, mean (SD)	24.7 (7.0)	25.4 (5.9)	23.6 (5.8)	3.1	0.04
Y-BOCS obsessions total score, mean (SD)	12.4 (3.7)	13.2 (3.1)	12.9 (3.2)	1.9	0.2
Y-BOCS compulsions total score, mean (SD)	12.2 (4.0)	12.2 (3.8)	11.0 (4.2)	5.5	0.004
Hamilton Depression Rating Scale, mean (SD)	10.4 (6.2)	11.1 (6.4)	12.3 (6.6)	2.1	0.1
Hamilton Anxiety Rating Scale, mean (SD)	10.3 (5.5)	12.2 (6.6)	13.0 (7.3)	4.0	0.02

The early ADO patients had a higher prevalence of male subjects and were younger. They also had a lower rate of employment compared to late ADO patients. Considering the Y-BOCS items, early ADO patients had a higher rate of religious obsessions. The rates of obsessions with need for symmetry or exactness and of repeating compulsions were marginally significantly higher in early ADO patients. All these results are summarized in Table 3. The multinomial logistic regression model, correcting for illness duration, confirmed the patterns of association identified with the univariate analysis, with the exception of obsessions with need for symmetry or exactness and of repeating compulsions for ADO subgroups and of type of clinical course, obsessions with need for symmetry and exactness, cleaning/washing, repeating, counting and hoarding/collecting compulsions for ASO subgroups.

Table 3. Comparison of clinical correlates between age at diagnosis onset subgroups in 483 obsessive compulsive disorder patients.

Clinical variable	Early age at diagnosis onset (*N*=369)	Late age at diagnosis onset (*N*=114)	$\chi 2$ or *t*	*p*
Female (%)	44.2 (163)	60.5 (69)	9.3	0.002
Employment status (%)	40.7 (150)	60.5 (69)	13.9	<0.0001
Presence of family history of OCD (%)	19.5 (72)	21.9 (25)	0.3	0.6
Presence of family history of mood disorders (%)	31.7 (117)	32.5 (37)	0.02	0.9
Presence of family history of anxiety disorders (%)	11.9 (44)	12.3 (14)	0.01	0.9
Mode of onset				
Abrupt (%)	27.6 (102)	34.2 (39)	1.8	0.2
Insidious (%)	72.4 (267)	65.8 (75)		
Type of clinical course				
Episodic (%)	14.6 (54)	21.9 (25)	3.4	0.07
Chronic (%)	85.4 (315)	78.1 (89)		
Current comorbidity with a psychiatric disorder (%)	69.6 (257)	69.3 (79)	0.005	0.9
Lifetime comorbidity with a psychiatric disorder (%)	78.9 (291)	78.9 (90)	0.0001	1
Current comorbidity with mood disorders (%)	53.1 (196)	61.4 (70)	2.4	0.1
Lifetime comorbidity with mood disorders (%)	61.0 (225)	69.3 (79)	2.6	0.1
Current comorbidity with anxiety disorders (%)	17.9 (66)	21.1 (24)	0.6	0.4
Lifetime comorbidity with anxiety disorders (%)	24.4 (90)	28.9 (33)	0.9	0.3
Comorbidity with tic disorder (%)	8.1 (30)	5.3 (6)	1.0	0.3
Personality disorders (%)	54.2 (169)	53.3 (48)	0.02	0.9
Cluster A (%)	13.5 (42)	11.1 (10)	0.3	0.6
Cluster B (%)	17.9 (56)	13.3 (12)	1.1	0.3
Cluster C (%)	35.9 (112)	33.3 (30)	0.2	0.6
Y-BOCS-Aggressive obsessions (%)	56.4 (206)	57.1 (64)	0.2	0.9
Y-BOCS-Contamination obsessions (%)	51.2 (187)	57.1 (64)	1.2	0.3
Y-BOCS-Sexual obsessions (%)	23.0 (84)	16.1 (18)	2.5	0.1
Y-BOCS-Hoarding/Saving obsessions (%)	17.5 (64)	12.5 (14)	1.6	0.2
Y-BOCS-Religious obsessions (%)	25.5 (93)	13.4 (15)	7.1	0.008
Y-BOCS-Obsessions with need for symmetry or exactness (%)	51.2 (187)	39.3 (44)	4.9	0.03
Y-BOCS-Somatic obsessions (%)	29.3 (107)	33.0 (37)	0.6	0.4
Y-BOCS-Cleaning/Washing compulsions (%)	55.1 (201)	57.1 (64)	0.1	0.7
Y-BOCS-Checking compulsions (%)	66.6 (243)	72.3 (81)	1.3	0.2
Y-BOCS-Repeating compulsions (%)	54.5 (199)	43.8 (49)	4.0	0.05
Y-BOCS-Counting compulsions (%)	21.4 (78)	17.9 (20)	0.6	0.4
Y-BOCS-Ordering/Arranging compulsions (%)	30.0 (109)	25.9 (29)	0.7	0.4
Y-BOCS-Hoarding/Collecting compulsions (%)	15.6 (57)	12.5 (14)	0.7	0.4
Age, mean (SD)	31.3 (10.9)	44.6 (10.3)	−11.5	<0.0001
Years of education, mean (SD)	12.5 (3.9)	12.3 (4.0)	0.4	0.7
Y-BOCS total score, mean (SD)	25.0 (6.3)	24.8 (5.4)	0.2	0.8
Y-BOCS obsessions total score, mean (SD)	13.0 (3.3)	13.1 (3.0)	−0.2	0.8
Y-BOCS compulsions total score, mean (SD)	12.0 (4.1)	11.8 (3.5)	0.5	0.6
Hamilton Depression Rating Scale, mean (SD)	10.8 (6.3)	12.5 (6.4)	−2.5	0.01
Hamilton Anxiety Rating Scale, mean (SD)	11.8 (6.5)	12.6 (6.7)	−1.0	0.3

4. Discussion

We found a bimodal distribution for ADO, but a trimodal distribution for the ASO. Furthermore, we observed that the ASO and the ADO distributions differed significantly.

Several findings deserve a comment. Admixture analysis of ADO was used previously by three independent groups. Consistently with our results, these studies reported that ADO had a bimodal distribution, although there was substantial between-study heterogeneity in the identified patients' subgroups both in terms of clinical characteristics and of proportion of individuals included in each AAO subgroup.

Specifically, Delorme et al. (2005) found in 161 OCD patients that the observed distribution of AAO was a mixture of two normal distributions with mean AAO of 11.1±4.1 and 23.5±11.1 years, respectively and a cut off of 20 years. Compared to late onset OCD, the EO subgroup (87.5% of the subjects) had a higher frequency of Tourette's disorder(26.9%) and of family history of OCD (24.6%). Conversely, LO OCD patients (12.5% of the sample) showed a higher prevalence of generalized anxiety disorder and major depressive disorder. Similarly, De Luca et al. (2011) found a bimodal distribution of ADO in 196 OCD patients (cut off at 15 years) although with different population proportions (55.4% for the EO and 44.6% for the LO) as well as with diverse clinical characteristics: mean AAO of 9.7±3.1 years for the EO and of 21.1±8.4 for the LO groups. Furthermore, the EO group was associated with longer duration of untreated illness. Finally, Anholt et al. (2014), replicated the finding of a bimodal distribution of AAO in 377 OCD patients, with a cut-off at 20 years, very similar to that of the Delorme study. However, the population proportions of the EO and LO subgroups, as well as their clinical characteristics, differed substantially from those identified in the Delorme study. Specifically, Anholt et al. reported higher mean AAO for EO and LO subgroups, as well as higher severity of symptoms on all OCD dimensions, along with a higher rate of ADHDsymptoms and of bipolar disorder in the EO subgroup.

Taken together, these findings support the use of admixture analysis of AAO in OCD samples as a mean to decrease the clinical heterogeneity of the disorder. But they also highlight the discrepancies existing in the classification of patients in each specific AAO subgroup. The different population proportions attributed to EO subgroup (e.g. 87.5% versus 55.4% versus 61%) do raise the question of whether clinical differences exist between subjects enrolled in the three studies. Moreover, clinical differences found between the EO and LO groups do not coincide. As an example, higher rates of major depressive disorder and generalized anxiety disorder were found in the LO group in the Delorme et al. (2005) study, while no differences were identified in the Anholt et al. (2014)study.

Several other studies, which did not use admixture analysis but rather defined a prioriand arbitrarily the AAO cut off points for the classification of patients, found differences between subgroups based on ADO, supporting the usefulness of AAO as a clinical specifier. Earlier onset has been associated with male gender (Fontenelle et al., 2003, Geller et al., 2001, Hanna, 1995, Mancebo et al., 2008, Swedo et al., 1989 and Zohar et al., 1997), greater familiality for OCD (Flament et al., 1988, Kessler et al., 2005, Nestadt et al., 2000, Pauls et al., 1995, Valleni-Basile et al., 1994 and Walitza et al., 2010), tic disorders (Chabane et al., 2005, Eichstedt and Arnold, 2001, Grados et al., 2001, Miguel et al., 2001 and Swedo et al., 1989), and obsessive–compulsive personality disorder(OCPD) (Maina et al., 2008). However, other clinical studies that used empirically defined AAO cut off points failed to confirm some of the previously mentioned associations of clinical correlates with specific AAO subgroups. For instance, some studies found no differences in gender prevalence (Janowitz et al., 2009, Millet et al., 2004, Rosario-Campos et al., 2001 and Sobin et al., 2000), while others failed to detect higher rates of tics in EO cases (Douglass et al., 1995).

Another clinically significant research question raised by this amount of evidence concerns the use of ASO or ADO (i.e. when symptoms interfere with patient's functioning) as best discriminative AAO. Specifically, we hypothesized that ASO might be more informative than ADO and tested

whether ASO and ADO had different distributions and identified different subgroups of OCD patients.

Accordingly, we studied a large and well-characterized sample of 483 subjects with a primary diagnosis of OCD, to date, the largest sample of patients investigated with admixture analysis of AAO. We found that both the mean ASO and the mean ADO were consistent with those reported in the literature (Angst et al., 2004, Dell'Osso et al., 2013 and Ruscio et al., 2010). Specifically, the mean ASO of our sample is consistent with other ASO found in community patients with obsessive–compulsive syndromes (16.9 years) and obsessive–compulsive symptoms (18.2 years) in Zurich (Angst et al., 2004). Furthermore, the AAO in our sample is similar to the mean AAO of 20.6 years found in a recent multicenter naturalistic study performed on 375 patients worldwide as part of the International College of Obsessive–Compulsive Spectrum Disorders (ICOCS) network (Dell'Osso et al., 2013) and with those found in epidemiological studies (Ruscio et al., 2010).

Concerning the AAO of OCD, we replicated findings of previous studies showing that AAO does not have a normal distribution, but rather is best described by a bimodal distribution (Anholt et al., 2014, De Luca et al., 2011 and Delorme et al., 2005) (Table 4). However, our AAO cut off of 26 years is different from those of the other studies which used the same methodology (20 years in the Delorme study, 15 in the De Luca one and 19 in that of Anholt and colleagues). Proportions of individuals allocated to each group (EO versus LO), then, differed between the studies, and this contributed to discrepancies in the clinical profiles of eAAO subgroups in different studies. It is possible that different clinical populations were recruited in different studies, and future investigations should include, to our opinion, patients from different centers. No previous studies examined ASO, thus a comparison with available evidence is difficult. Our finding that ASO and ADO showed different distributions: trimodal for ASO and bimodal for ADO raises the question of whether ASO might be a best discriminator between homogeneous subgroups of patients for the investigation of potential differences in risk factors (genetic and environmental) than ADO. Future studies, should look at both ASO and ADO.

Table 4. Comparison of results between the present and previously published studies of admixture analysis of ADO in OCD samples.

Study	Sample (*N*)	EO group (mean ADO; proportion of the sample; cut-off age)	LO group(mean ADO; proportion of the sample; cut-off age)	Associated clinical characteristics
Delorme et al. (2005)	161	11.1±4.1 yrs	23.5±11.1 yrs	EO: increased rates of Tourette's syndrome and OCD in family membersLO: increased rate of MDD and GAD
		87.5%	12.5%	
		≤20 yrs	>20 yrs	
De Luca et al. (2011)	196	9.7±3.1 yrs	21.1±8.4 yrs	Earlier AAO associated with longer DUI
		55.4%	44.6%	
		≤15 yrs	>15 yrs	
Anholt et al. (2014)	377	12.8±4.9 yrs	24.9±9.3 yrs	EO: more symptoms on al OCD dimensions, increased rates of ADHD and BD
		61%	39%	
		≤19 yrs	>19 yrs	
Present study	483	18.0±4.5 yrs	29.5±10.3 yrs	EO: more males, lower employment rate; more religious obsessions
		64%	36%	
		≤26 yrs	>26 yrs	

EO=Early-onset; LO=Late-onset
ADO=age at disorder onset
MDD=major depressive disorder; GAD=generalized anxiety disorder
DUI=duration of untreated illness
ADHD=attention deficit and hyperactivity disorder; BD=bipolar disorder; OCD=obsessive compulsive disorder

We confirmed that the subgroups according to ASO and ADO have different clinical profiles. When ASO was considered to differentiate three groups (early-versus intermediate- versus late-onset), several peculiar characteristics emerged: the EO group (ASO≤9 years) exhibited more religious obsessions, obsessions with need for symmetry/exactness, cleaning/washing, repeating, counting and hoarding compulsions. The LO subgroup (ASO≥24 years) had more frequently an abrupt onset of the disorder (52% of cases), and an episodic course (28% of subjects); considering the mean YBOCS total and compulsion scores, they also appeared less severe at the time of inclusion in the study.

When subgroups were examined according to ADO, the EO subgroup (ADO≤26 years) was characterized by a higher proportion of males, a possible greater disability (lower proportion of subjects employed), and higher expression of religious obsessions, obsessions with need for symmetry/exactness, repeating compulsions. No differences emerged in family history, presence of tics, Axis I and II comorbidities.

Our study replicated and extended previous findings showing that subgroups according to AAO are different in terms of clinical profiles and could be influenced by distinct genetic susceptibility and/or environmental risk factors. Age at onset, whether ASO or ADO, represents a relevant clinical feature that might enhance the clinical delineation of OCD patients.

Strengths of our study are, firstly, the inclusion of the largest sample of OCD patients to date (N=483); moreover, patients were carefully clinically characterized, and this allowed us to investigate several different clinical features, including Axis I comorbidities and personality disorders. We also added to the existing literature by including ASO and ADO.

5. Limitations

Limitations of our study, on the contrary, are the retrospective investigation of AAO, which is subject to recall bias. We tried to limit this bias by investigating the patient carefully, having in all possible cases another informant (generally a family member) confirming the AAO, and by examining medical records of patients. Another limitation is that our sample may not represent the OCD population, as we enrolled patients referring to a tertiary center specialized in the treatment of OCD. Results will need then to be confirmed in community samples. A third limitation is that we could not examine medication status (e.g. the proportion of patients in each group drug-naive at enrollment in the study); this raises the possibility that some of the observed differences (severity of OC symptoms, as measured by the YBOCS, for example, but not other clinical characteristics such as mode of onset or lifetime OC dimensions) might be due to treatment received previously or to current treatment.

Notwithstanding these limitations, our results support the notion that AAO may be a key phenotypic characteristic in elucidating the genetic architecture of OCD as well as the possible environmental influences that might add to its genetic liability threshold. We found that ASO and ADO had different distributions and identified different subgroups of OCD patients. We suggest that 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.

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