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A cluster analysis of early onset in common anxiety disorders

A. Schat (PhD)[a,*], M.S. van Noorden (M.D., PhD)[a], M.J. Noom (PhD)[b,c], E.J. Giltay (M.D., PhD)[a], N.J.A. van der Wee (M.D., PhD)[a], R. de Graaf (PhD)[d], M. ten Have (PhD)[d], R.R.J.M. M. Vermeiren (M.D., PhD)[e], F.G. Zitman (M.D., PhD)[a]

[a] Leiden University Medical Center, Department of Psychiatry, P.O. Box 7500, 2300 RC Leiden, The Netherlands
[b] Zaans Medisch Centrum, Department of Psychiatry, Kon. Julianaplein 58, 1502 DV Zaandam, The Netherlands
[c] Mental Health Center GGZ Eindhoven, dept. of child and adolescent psychiatry, Doctor Poletlaan 40, 5626 ND Eindhoven, The Netherlands
[d] Netherlands Institute of Mental Health and Addiction, P.O. Box 725, 3500 AS, Utrecht, The Netherlands
[e] Department of Child and Adolescent Psychiatry, Curium-Leiden University Medical Center, Endegeesterstraatweg 27, 2342 AK Oegstgeest, The Netherlands

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ABSTRACT

Early onset is regarded as an important characteristic of anxiety disorders, associated with higher severity. However, previous findings diverge, as definitions of early onset vary and are often unsubstantiated. We objectively defined early onset in social phobia, panic disorder, agoraphobia, and generalised anxiety disorder, using cluster analysis with data gathered in the general population. Resulting cut-off ages for early onset were ≤22 (social phobia), ≤31 (panic disorder), ≤21 (agoraphobia), and ≤27 (generalised anxiety disorder). Comparison of psychiatric comorbidity and general wellbeing between subjects with early and late onset in the general population and an outpatient cohort, demonstrated that among outpatients anxiety comorbidity was more common in early onset agoraphobia, but also that anxiety- as well as mood comorbidity were more common in late onset social phobia. A major limitation was the retrospective assessment of onset. Our results encourage future studies into correlates of early onset of psychiatric disorders.

1. Introduction

Age of onset (AOO) is seen as an important clinical characteristic of psychiatric disorders (Kessler et al., 2007). Anxiety disorders typically emerge early in life. Social phobia (SP) often develops in childhood or adolescence (Beesdo, Knappe, & Pine, 2009; Craske, 1999; Kessler et al., 2007; Scheibe & Albus, 1992; Thyer, Parrish, Curtis, Nesse, & Cameron, 1985). Panic disorder (with/without agoraphobia; PD) and agoraphobia (without panic; AP) usually start in adolescence through mid-adulthood (Beesdo et al., 2009; Craske, 1999; Kessler et al., 2007; Thyer et al., 1985). Finally, for generalised anxiety disorder (GAD), adolescent-/early adult- (Beesdo et al., 2009; Scheibe & Albus, 1992), as well as mid adult- (Kessler et al., 2007; Thyer et al., 1985), and late adult onset are common (Craske, 1999). Anxiety disorders that have an early onset are thought to represent a subtype that is more severe. Early onset has been associated with higher symptom severity in SP (Van Ameringen, Oakman, Mancini, Pipe, & Chung, 2004), PD (Segui et al., 2000; Tibi et al., 2013), and GAD (Le Roux, Gatz, & Wetherell, 2005), more psychiatric comorbidity in PD (Goodwin, Lipsitz, Chapman, Mannuzza, & Fyer, 2001; Goldstein, Wickramaratne, Horwath, & Weissman, 1997; Ramsawh, Weisberg, Dyck, Stout, & Keller, 2011; Segui et al., 1999; Tibi et al., 2013) and GAD (Campbell, Brown, & Grisham, 2003; Le Roux et al., 2005), and more suicidality in PD (Iketani et al., 2004), although contradictory findings have also been reported (Iketani et al., 2004; Le Roux et al., 2005; Segui et al., 1999, 2000).

These inconsistencies might be attributed to variations in definitions of early onset (Tibi et al., 2013). AOO has been approached as a continuous variable in SP (Van Ameringen et al., 2004), GAD (Campbell et al., 2003), and PD (Goodwin et al., 2001); but also through unsubstantiated cut-off ages, covering a wide age-range from 9 (Van Ameringen et al., 2004) and 20 (Ramsawh et al., 2011) in SP; 18 (Segui et al., 1999), 20 (Goldstein et al., 1997; Ramsawh et al., 2011), 25 (Iketani et al., 2004), and 60 (Segui et al., 2000) in PD; and 20 (Ramsawh et al., 2011) and 50 (Le Roux et al., 2005) in GAD. The use of objectively determined cut-offs to define early onset could benefit comparability of findings, as well as their trans-

Abbreviations: AOO, age of onset; SP, social phobia; PD, panic disorder with or without agoraphobia; AP, agoraphobia without panic; GAD, generalised anxiety disorder; NEMESIS-2, Netherlands Mental Health Survey and Incidence Study-2; ROM, Routine Outcome Monitoring.

* Corresponding author.
E-mail address: a.schat@lumc.nl (A. Schat).

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lation to clinical practice. One method to empirically define age cut-offs for early- and late onset in various psychiatric disorders is model based clustering (Albert et al., 2015; Anholt et al., 2014; Bauer et al., 2010; Bellivier, Golmard, Henry, Leboyer, & Schurhoff, 2001; Delorme et al., 2005; Hamshere et al., 2009; Ortiz et al., 2011; Panariello et al., 2010; Tibi et al., 2013, 2015; Tozzi et al., 2011; Zhu et al., 2012). If early onset anxiety is a naturally occurring subtype within anxiety disorders, the distribution of AOO of this subtype will be Gaussian (Delorme et al., 2005). Therefore, when describing the AOO frequency distribution per disorder, separate normal distributions should emerge. Cut-points of the distributions can then be used to determine cut-offs for early onset. Cluster analysis can be used to define the number of distinct normal distributions that best fits the AOO frequency distribution. In anxiety disorders, previous application of cluster analysis has resulted in cut-offs of 27 years for PD (Tibi et al., 2013) and AP (Tibi et al., 2015). In these studies prevalence of AP and childhood trauma was higher in early onset PD (Tibi et al., 2013) and early onset AP was associated with first-degree family history of anxiety disorders (Tibi et al., 2015). To date, to our knowledge, early onset of SP and GAD has not been described using cluster analysis.

In the present study we applied cluster analysis to AOO data gathered in a large general population study to estimate early onset cut-offs for PD, AP, SP, and GAD. Subsequently, we compared psychiatric comorbidity as well as general wellbeing in subjects with early- and late onset. In order to identify the relevance of early onset for clinical practice, this comparison was repeated in an outpatient sample. Based on previous studies (Campbell et al., 2003; Goldstein et al., 1997; Goodwin et al., 2001; Iketani et al., 2004; Le Roux et al., 2005; Ramsawh et al., 2011; Segui et al., 1999, 2000; Tibi et al., 2013, 2015; Van Ameringen et al., 2004), we hypothesized that early onset would be associated with more psychiatric comorbidity and less wellbeing.

2. Materials and methods

2.1. Participants

AOO frequency data were collected in The Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2), a large epidemiologic survey in the Dutch general population ages 18–64. The first wave ran between November 2007 and July 2009. Structured interviews were conducted during house visits by trained- and supervised lay-interviewers. The response percentage was 65% and the sample adequately represented the Dutch population (de Graaf, ten Have, & van Dorsselaer, 2010). Respondents provided written informed consent and the study design was approved by the METIGG, a national mental healthcare ethics committee in The Netherlands. A more detailed description of the NEMESIS-2 design can be found in de Graaf et al. (2010). Although the NEMESIS-2 sample reflected the Dutch population well, younger subjects were slightly under-represented, therefore, NEMESIS-2 data were weighted in analyses (de Graaf et al., 2010).

For the comparison of psychiatric comorbidity and general wellbeing between subjects with early- and late onset anxiety, in addition to the NEMESIS-2 general population sample, we used clinical data from the Leiden Routine Outcome Monitoring (ROM) Study. The Leiden ROM Study is a naturalistic study among outpatients at Rivierduinen, a regional mental healthcare provider, and at the department of psychiatry of the Leiden University Medical Centre in The Netherlands. Both centres treat patients who have been referred by their general practitioner for specialized treatment of mood-, somatoform- or anxiety disorders. As part of routine clinical practice, all patients between ages 18 and 65 were administered an extensive battery of diagnostic and psychometric measures by trained research nurses or through supervised computerized self-report. This procedure is known as ROM and is described in more detail by de Beurs et al. (2011). Inclusion during the study period January 2004 and September 2012 was estimated at 80% (van Noorden et al., 2011; Zitman, 2012). Data were anonymised and the ethical review board at the Leiden University Medical Centre approved their use in scientific research.

2.2. Measures

In the NEMESIS-2 sample, diagnostic information was collected using the Composite International Diagnostic Interview 3.0 (CIDI-3.0) (Kessler & Ustun, 2004). The CIDI-3.0 has good validity (Haro et al., 2006). studies of earlier versions of the CIDI demonstrated good reliability with inter-rater reliabilities above 0.94 for anxiety disorders (Wittchen et al., 1991) and test-retest reliability above 0.57 for all anxiety disorders except GAD ($\kappa = 0.41$) (Semler et al., 1987). In ROM, diagnostic information was collected with the MINI International Neuropsychiatric Interview-Plus (MINI-Plus) (Sheehan et al., 1998; van Vliet, Leroy, & van Megen, 2000). The MINI-Plus also has good psychometric properties, with inter-rater reliability between 0.88 and 1.00; test-retest reliability between 0.76 and 0.93; and adequate validity compared to the CIDI-1.0 (Lecrubier et al., 1997). The CIDI-3.0 and MINI-Plus were used to ascertain current (12-month) and lifetime Diagnostic Statistical Manual fourth edition (DSM-IV) (NEMESIS-2) and DSM-IV-text revision (DSM-IV-TR) (ROM) anxiety disorders (including post-traumatic stress disorder, specific phobia, and obsessive compulsive disorder), comorbid depressive and dysthymic disorders, and alcohol- and drug abuse and dependence. As in both samples all diagnostic information was collected through diagnostic screening instruments, no distinctions between primary and secondary diagnoses could be made.

In both the CIDI-3.0 and the MINI-Plus, AOO of anxiety disorders was assessed. In the MINI-plus, after confirming (past or present) diagnosis, the patient was asked: “How old were you when you first experienced these symptoms?” In the CIDI-3.0, after confirming (past or present) diagnosis, the subject was asked: “Can you remember your exact age the very first time you experienced these symptoms?” If the subject did not provide an exact age, he/she was asked to provide an estimate. If the answer remained inconclusive, the subject was asked whether this occurred before the first year of school (AOO = 4), before puberty (AOO = 12) or not before puberty (AOO = 13). For subjects who could not provide an AOO or stated that the disorder had always been present, AOO was considered missing.

In both samples general wellbeing was examined using the subscale general health perception of the Dutch version of the Short Form-36 (SF-36) (Aaronson et al., 1998), a 36-item self-report survey. Measurement scales vary, ranging from yes/no to answers on a 3-, 5- or 6-point Likert-scale. Raw scores are linearly converted to 0–100 subscales, with higher scores representing higher levels of wellbeing. The SF-36 general health perception scale has moderate to good psychometric properties (Cronbach’s alphas between 0.76 and 0.78 (Aaronson et al., 1998)). To facilitate interpretation, we used reference cut-off values for the general population (Schulte-van Maaren et al., 2012), with scores below the cut-off of 45 indicating poor functioning, and scores above the cut-off being in the normal range.

2.3. Statistical analyses

We applied ‘mclust module version 5.0.2 for R: normal mixture modelling for model-based clustering, classification and density estimation’ (Fraley & Raftery, 2002; Fraley, Raftery, Murphy, & Scrucca, 2012) to the AOO data of NEMESIS-2 subjects with life-