Psychiatry Research 216 (2014) 351–356

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Family load estimates and risk factors of anxiety disorders in a nationwide three generation study

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ARTICLE INFO

Article history:
Received 6 March 2013
Received in revised form
9 February 2014
Accepted 14 February 2014
Available online 24 February 2014

Keywords:
Anxiety disorder
Early onset
Family based register study

ABSTRACT

The present study investigated how often anxiety disorders with different ages of onset occurred in affected families compared to control families. Furthermore, the study addressed the impact of sex, region of residence, year and month of birth, and parental age at birth. The sample included $N=1373$ child and adolescent psychiatric participants born between 1952 and 2000 and registered in the Danish Psychiatric Central Register (DPCR) who developed an anxiety disorder before the age of 18. $N=4019$ controls without any psychiatric diagnosis before age 18, were matched for age, sex, and residential region. Psychiatric diagnoses were also obtained for parents, siblings, and offspring. A family load component was obtained by using various mixed regression models. Anxiety disorders occurred significantly more often in case than in control families. Having a mother, father, or a sibling with the disorder was proven to be a risk factor. Female sex, year of birth, and region of residence were also associated with having an anxiety disorder. Furthermore, case relatives did not develop an anxiety disorder earlier than control relatives. These findings, based on a very large and representative dataset, provide further and solid evidence for the family aggregation of anxiety disorders.

1. Introduction

According to various international surveys, anxiety disorders (ANX) are the most frequently diagnosed disorders in childhood and adolescence with girls affected more frequently than boys (Steinhausen et al., 1998; Costello et al., 2005). Anxiety disorders are still very common in adulthood, with prevalence estimates ranging between 10% and 25% (Alonso et al., 2004; Somers et al., 2006), with a higher prevalence in women (Somers et al., 2006), and a lifetime prevalence of 25% (Kessler et al., 1994; Hettema et al., 2001). Furthermore, in all age groups ANX are highly co-morbid with each other and with other psychiatric disorders, in particular mood disorders (Maser and Cloninger, 1990; Hettema et al., 2001; Costello et al., 2005; Ollendick and Seligman, 2006).

Several studies have documented a strong familial aggregation of either anxiety disorders in general or specific anxiety disorders or phobias (Noyes. et al., 1986; Last et al., 1991; Mendlewicz et al., 1993; Fyer et al., 1995; Stein et al., 1998; Lieb et al., 2000; Hettema et al., 2001; Li et al., 2008; Low et al., 2008; Steinhausen et al., 2009). A comprehensive review and meta-analysis of the genetic epidemiology of ANX, (Hettema et al., 2001) found that odds ratios predicting association of illness in first-degree relatives and affection status of the proband (disorder present or. absent) were homogeneous across studies for all disorders. The calculated summary odds ratios ranged from 4 to 6, depending on the disorder.

In accordance with this estimation, a more recent study based on register data for three generations in Denmark (Steinhausen et al., 2009) showed that case-probands and first degree relatives were significantly more likely to exhibit the same diagnosis for anxiety disorders. A recent study (Li et al., 2008) based on Swedish register data investigated a cohort of sons and daughters with at least one affected parent with any anxiety disorder. This study showed that if one parent had an anxiety disorder, the standardised incidence rate was around 2, indicating an increased occurrence of the disorder in the child as well. If both parents had an anxiety disorder the risk associated with it occurring in the offspring increased to 5.1. Another nationwide study based on hospital records in Sweden by (Li et al., 2011) concluded that the sibling risk of being diagnosed with an anxiety disorder was 2.26 and that the risk was independent of age

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http://dx.doi.org/10.1016/j.psychres.2014.02.026
0165-1781

and sex differences between siblings. Furthermore, the risk was highest in siblings under 20 years and higher among female than in male siblings.

Various characteristics of the family aggregation have been elucidated. Some previous studies on generalized anxiety disorder have been inconclusive on whether or not relatives of probands with generalized anxiety disorder are more likely to develop the same anxiety disorder or another anxiety disorder like, for example, panic disorder, phobia or another ANX (Mendlewicz et al., 1993; Coelho et al., 2007). However, in the Danish three-generation study (Steinhausen et al., 2009), probands and first-degree relatives were significantly more likely to exhibit the same anxiety disorders. Furthermore, the Swedish register study (Li et al., 2008) demonstrated that maternal transmission of anxiety was higher than paternal transmission and that the degree of parental transmission was similar for men and women.

Given the influence that demographic factors have in general on the epidemiology of mental disorders, one wonders whether or not these factors also play a role in the family aggregation of the ANX. For instance, a recent meta-analysis of urban–rural differences in prevalence rates calculated a pooled urban–rural odds ratio (*OR*) for the total prevalence of anxiety disorders with a significantly higher *OR* in urban compared to rural areas (Peen et al., 2010). Furthermore, higher levels of urbanization were linked to higher 12-month prevalence rates of ANX in another recent study (Dekker et al., 2008). However, so far, no study has controlled for any urbanization effects in the family aggregation of the ANX. Whereas other risk factors like parental age at birth or age of onset of the disorder in the probands have been considered for instance in family studies of schizophrenia (Helenius et al., 2012) and bipolar disorders (Helenius et al., 2013), it is unknown whether these risk factors are associated also with the family aggregation of the ANX.

The present register-based study deals with the family aggregation of ANX as part of the Danish three generations study based on a matched case-control dataset. Previous publications have dealt with an overall assessment of family aggregations across all diagnoses in the entire study samples (Steinhausen et al., 2009) and the measurement of the specific aggregation by use of a new measure of the family load in schizophrenia (Helenius et al., 2012), bipolar disorders (Helenius et al., 2013), and obsessive-compulsive disorders (Steinhausen et al., 2013). Because there is evidence of specificity in the family transmission of phobic disorders and ANX (Fyer et al., 1995; Coelho et al., 2007; Low et al., 2008) the issue of the family aggregation of the phobic disorders was not included in the present contribution.

The aim of the present study was to investigate how often ANX occur in affected families compared to control families by calculating a family load component. The latter measures the degree of dependence among family members in relation to the outcome. Furthermore, the study addressed the association of maternal and paternal age at birth, and age at onset with the family aggregation of ANX. In addition, the study was controlled for the matching variables sex, month and year of birth, and region of residence with the understanding that these variables might also have an impact on the family aggregation of ANX. Finally, whether case family members develop ANX earlier than control family members was also investigated.

2. Methods

2.1. Description of the dataset

The dataset of the present study contained $n=1373$ case families with each family including one case-proband who was identified in the Danish Psychiatric Central Registry (DPCR) (Munk-Jorgensen & Mortensen, 1997). Case-probands were born between 1952 and 2000. They had developed ANX before the age of 18, as either a main or a secondary diagnosis. In Denmark each individual is given an individual number at birth in the Danish Central Register (DCR) making it possible to identify each person in various registers (Pedersen et al., 2006).

For each case-proband three control-probands were identified in the DCR. Control-probands ($n=4019$) were identified in the DCR using risk set sampling, that is they were alive and without registrations in the DPCR at the case-probands index time. Furthermore, the control-probands were matched to the case-probands by age (same year and month of birth), sex, and region of residence. Because controls were matched before identifying them in the psychiatric register some control-probands fulfilled the case definition, i.e. had a psychiatric diagnosis before age 18; these subjects were deleted from the study along with those controls that developed ANX after age 18. Consequently, a total of $n=98$ of the case-probands had less than three control-probands.

In total, the dataset contained $n=5392$ probands corresponding to the number of families included in the study. Family members were identified in the DCR and were participants in the Danish Three Generation Study (3GS) with several ten thousands of each case-probands, control-probands, parents, siblings, and offspring (Steinhausen et al., 2009). The numbers of family members in the present study will be shown with the results. Participants were followed from birth or from January 1st, 1969, when the DPCR was computerized, until December 1st, 2009 providing an observation period with a maximum of 40 years.

For all family members, ANX were counted as main or up to three secondary diagnoses, and were defined according to ICD-8 criteria (code 300.0, anxiety neurosis) until 1993, or ICD-10 criteria (code F41 including F41.0 panic disorder, F41.1 generalized anxiety disorders, F41.2 mixed anxiety and depressive disorder, F41.3 other mixed anxiety disorders, F41.8 other specified anxiety disorders, F41.9 anxiety disorder unspecified and the child-specific category of F93.0 separation anxiety disorder) since 1994 (World Health Organization, 1992; World Health Organisation, 1967) $n=1131$ (82.37%) of the case-probands had a lifetime diagnosis of ANX as a main diagnosis while $n=242$ (17.63%) had the diagnosis as a secondary diagnosis during the observation period which ended December 2009. A total of 86.68% of the ANX diagnoses were based on ICD-10 criteria while 13.32% of the diagnoses were assigned according to ICD-8 criteria. All diagnoses were based on assessment of psychopathology by clinical psychiatrists at the time when the patients were in clinical care.

2.2. Statistical analyses

Analyses were based on χ^2-tests and various types of regression modelling, i.e. conditional logistic regression, mixed logistic regression and survival analysis (Cox regression with shared frailty). χ^2-tests were applied to the data to determine if ANX occurred more often in the case population than in the control population when stratifying on the family members.

Conditional logistic regression was applied to determine if the status of certain family members increases the risk of the disorder in the case-probands more than others by including three indicator variables (paternal ANX, maternal ANX and sibling ANX) each representing whether or not a certain family member has ANX. If data from a family member were missing the value of the variable was 0. Since this method takes matching into account, the matched variables were not included in the analysis whereas maternal and paternal age at birth was included. All variables were included as categorical variables. Maternal age at birth was divided into 5 groups, namely, <20, 20–24, 25–19, 30–34 and ≥ 35 years while paternal age at birth was divided into the groups <20, 20–24, 25–34, 35–39 and ≥ 40 years. In these analyses, maternal age at birth was missing in 126 families whereas paternal age at birth was missing in 233 families. This was due to the fact that in some families neither a mother nor a father was registered. The definite analyses included $N=4986$ families.

Mixed logistic regression was applied to estimate a family load component. This family load component was estimated as a random effect. The random effect measures the dependence among the family members in relation to how often each family developed ANX. The random effect was divided into groups, namely, cases and controls. Furthermore, the regression analysis included the matched explanatory variables, i.e., sex, year of birth, month of birth, and region of residence. The latter was converted into a dichotomous variable comparing the capital of Copenhagen to all other regions. Sex, month of birth, and region of residence were included as categorical variables while year at birth was included as a continuous variable.

Cox regression with shared frailty was applied to investigate if case family members developed ANX earlier than control family members, i.e. the probands were excluded from the analysis. The family load component is estimated as a random effect (frailty). A frailty measures the dependence among the family members in relation to the time to disease onset implying that a family with a high value of the frailty developed ANX earlier than a family with a small value of the frailty. The frailty is assumed to follow the gamma distribution with a *mean* value of 1 and variance theta. The purpose of this approach is to estimate the effect of the explanatory variables while also estimating theta. The analysis included the matched explanatory variables sex, year and month of birth, and region of residence.