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Transition and remission in adolescents at ultra-high risk for psychosis

Tim B. Ziermans *, Patricia F. Schothorst, Mirjam Sprong, Herman van Engeland

Department of Child and Adolescent Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, The Netherlands

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ABSTRACT

Background; Future success of early intervention initiatives to prevent the onset of psychosis will rely on the validity of methods to predict clinical outcome. Proper identification is particularly essential for young adolescents, as psychotic-like symptoms are often transitory during this period and mislabeling can lead to early stigmatization and unnecessary treatment. This article presents results from a prospective, naturalistic 2-year follow-up study of a cohort of young adolescents putatively at ultra-high risk (UHR) for psychosis.
Methods; Seventy-two adolescents between 12 and 18 years were recruited, fulfilling either UHR criteria or the basic symptom-based criterion cognitive disturbances (COGDIS). Incidence of transition as well as the remission rate from UHR status was calculated. Individuals who made a transition (UHR-P) were compared to those who did not (UHR-NP) and to those who remitted (UHR-R) on socio-demographic and clinical characteristics.
Results; Fifty-seven UHR individuals completed the 2-year follow-up assessment. The confirmed transition rate was 15.6% and 35.3% still met UHR criteria. The remaining 49.1% had remitted from an initial UHR status. The UHR subgroups did not differ on socio-demographic or clinical variables at baseline.
Conclusions; Half of young adolescents meeting UHR criteria continue to experience prodromal or psychotic symptoms after 2 years. However, they are at least three times more likely to have remitted from their UHR status than to have made a transition to psychosis. In addition, baseline characteristics are not indicative of clinical outcome at follow-up. Our results emphasize the need for further improvement and stratification of relative risk factors for psychosis.

1. Introduction

The emergence of early intervention initiatives has rekindled the conviction that therapeutic efforts can make a significant contribution to the prevention of schizophrenia and psychotic disorders. However, successful implementation of treatment requires a high level of accuracy in identifying individuals at risk for developing psychosis to omit negative side effects (McGorry et al., 2009). The introduction of 'ultra-high risk' (UHR) and 'basic symptoms' criteria (Cornblatt et al., 2003; Klosterkötter et al., 2001; Yung et al., 2003) has provided international research groups with useful assessment tools to help identify young individuals who are 'prodromal' or putatively at risk. UHR criteria refer to a combination of: 1) Attenuated Positive Symptoms (APS); 2) Brief Limited Intermittent Psychotic Symptoms (BLIPS); 3) Trait plus state risk factor (Yung et al., 2003). With the basic symptoms approach self-experienced disturbances are assessed in a range of domains, such as cognition, perception, affect regulation and motor function (Klosterkötter et al., 2001; Schultze-Lutter, 2009). While there is substantial overlap between UHR and basic symptoms criteria, they can also be used in parallel to define a more homogeneous sample of clinically and cognitively impaired individuals (Simon et al., 2006). From here on the term *UHR* will be used in

* Corresponding author. Department of Neuroscience, Karolinska Institutet, Retzius Väg 8, A3-315b, 171 77 Stockholm, Sweden. Tel.: +46 852586394.
E-mail address: Tim.Ziermans@ki.se (T.B. Ziermans).

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reference to studies applying UHR and/or basic symptoms criteria.

UHR criteria have been relatively successful in identifying individuals at incipient risk of a psychotic transition. While the overall estimate of the 1-year transition rate is 36.7% (Ruhrmann et al., 2003), individual study sites have reported transition rates as low as 9% (Carr et al., 2000) and as high as 70% (Klosterkötter et al., 2001), with follow-up intervals ranging from 1 to 9.6 years (Cannon et al., 2008). Additionally, recent reports of declining transition rates (15–19%) have been attributed to earlier referral, effective treatment strategies and/or inclusion of a larger proportion of 'false positives' (Haroun et al., 2006; Ruhrmann et al., 2010; Yung et al., 2008).

Two recent studies on clinical remission in UHR individuals (Simon and Umbricht, 2010; Velthorst et al., 2010) showed that a 50–75% of UHR individuals between 12 and 40 years of age remit from their initial UHR status within 1 to 3 years post-inclusion. The authors concluded that symptoms may be transitory for a majority of UHR individuals which increases the chance of social stigma by mislabeling. This may particularly hold for individuals in the young adolescent phase, when prodromal and psychotic-like experiences are most likely to occur for the first time (Häfner, 1995; Häfner and Maurer, 2006). Prevalence of prodromal symptoms in typically developing adolescents can be relatively high (30%) (Meng et al., 2009) and show high levels of discontinuation (van Os et al., 2009; Escher et al., 2002; Simon et al., 2009). Because peak age of onset for psychotic disorders is estimated around the late teens/early twenties (Kessler et al., 2007), and early onset psychosis may represent more severe variants of the disorder (Amminger et al., 2006; Hollis, 2000), it is of critical importance to test the predictive validity of UHR criteria in adolescent cohorts (Borgmann-Winter et al., 2006).

The present report is an exploratory investigation of the clinical outcome of an adolescent UHR cohort from the Dutch Prediction of Psychosis Study (DUPS), a naturalistic longitudinal study (Sprong et al., 2008). Rates for transition and remission are discussed and baseline characteristics are compared for individuals with different clinical outcomes. It was hypothesized that a considerable amount of UHR adolescents would no longer meet UHR criteria at the 2-year follow-up assessment. Additionally, it was expected that clinical status at follow-up would be independent of any differences in socio-demographic and clinical characteristics at baseline.

2. Methods

2.1. Participants

All data were collected at the Child and Adolescent Psychiatry Department of the University Medical Center Utrecht. Participants were between 12 and 18 years of age at the time of recruitment and were included after informed consent was given. Individuals younger than 16 years of age signed for assent, while their parents signed for consent. Individuals aged 16 years or older provided informed consent themselves.

Participants were help-seeking adolescents referred by general practitioners or other psychiatric clinics, of which 72 individuals met UHR inclusion criteria. Inclusion criteria were adopted from the European Prediction of Psychosis Study (EPOS), a prospective multicenter study (Klosterkötter et al., 2005). Participants had to fulfil at least one of the following criteria: 1) attenuated positive symptoms (APS), 2) brief, limited, or intermittent psychotic symptoms (BLIPS), 3) genetic risk for psychosis, combined with a deterioration in overall level of social, occupational/school, and psychological functioning in the past year (GRD) and 4) two or more of a selection of nine basic symptoms used to assess mild cognitive disturbances (COGDIS). The COGDIS items have the highest predictive validity of all basic symptoms and have previously been associated with a transition rate to psychosis of 46.3% at 24 months (Schultze-Lutter et al., 2007). The first three inclusion criteria were assessed with the Structured Interview for Prodromal Syndromes (SIPS) and the accompanying Scale of Prodromal Symptoms (SOPS) (McGlashan et al., 2001; Miller et al., 1999). The fourth inclusion criterion was assessed with the Bonn Scale for the Assessment of Basic Symptoms-Prediction List (BSABS-P) (Schultze-Lutter and Klosterkötter, 2002).

Exclusion criteria consisted of a past or present psychotic episode lasting >1 week, traumatic brain injury or any known neurological disorder; verbal intellectual functioning (VIQ) <75. Drug abuse and alcohol abuse were additional exclusion criteria, although UHR subjects were permitted a history of drug use if symptoms had also been present in the absence of drugs. Alcohol and drug use was assessed with sections J and L of the composite international diagnostic interview (CIDI) (World Health Organization, 1993). Frequent use of cannabis was defined as ≥1 consumption per week.

Follow-up assessments were conducted 9, 18 and 24 months post-baseline to determine presence of a psychotic transition. A psychotic syndrome was operationalized as the presence of positive symptoms that are seriously disorganizing, i.e. a score of 6 on any of the items of the SIPS-Positive Symptoms subscales for a period of more than 7 days (Cannon et al., 2008; Ruhrmann et al., 2010). Chart reviews were used to retrospectively confirm psychotic transition by clinical consensus (HvE, PS) and psychotic subjects were subsequently diagnosed according to *DSM-IV* guidelines (American Psychiatric Association, 1994).

For our group analyses the UHR group was subdivided into individuals with subsequent psychotic transition (UHR-P), individuals with sustained UHR status at 24 months (UHR-NP) and those who had remitted from their UHR-status at 24 months (UHR-R). This study was not a treatment trial and did not involve a clinical intervention. When applicable, treatment as usual was continued between follow-up assessments.

2.2. Data analysis

All statistical analyses were performed with the Statistical Package for Social Science (SPSS 15.0) for Windows. Baseline data were examined using descriptive statistics. A Kaplan-Meier Survival Analysis was performed to assess rate of transition. For group comparisons (UHR-R vs UHR-NP vs UHR-P) of socio-demographic and clinical variables all data were checked for homogeneity and normality. In order to compare our results with a previous study (Simon and Umbricht, 2010), we also analyzed the results for the UHR-R