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Is it still correct to differentiate between early and very early onset psychosis?

Ashleigh Lin [a], Klaas J. Wardenaar [b], Maria Pontillo [c], Franco De Crescenzo [c], Luigi Mazzone [c], Stefano Vicari [c], Stephen J. Wood [d,e], Amanda Beavan [d], Marco Armando [c,f,*]

[a] Telethon Kids Institute, The University of Western Australia, 100 Roberts Road, Subiaco, 6008, Western Australia, Australia
[b] Department of Psychiatry, Interdisciplinary Center Psychopathology and Emotion Regulation (ICPE), University of Groningen, University Medical Center Groningen, The Netherlands
[c] Child and Adolescence Neuropsychiatry Unit, Department of Neuroscience, Children Hospital Bambino Gesù, Piazza Sant'Onofrio 4, 00165 Rome, Italy
[d] School of Psychology, University of Birmingham, Edgbaston B15 2TT, United Kingdom
[e] Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health, Level 3, Alan Gilbert Building, 161 Barry St, Carlton, Victoria 3053, Australia
[f] Office Médico-Pédagogique Research Unit, Department of Psychiatry, University of Geneva School of Medicine, Geneva, Switzerland

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ABSTRACT

Objective: It remains unclear whether very early onset psychosis (VEOP; ≤12 years of age) and early onset psychosis (EOP; onset 13–17 years of age) are homogeneous in their clinical presentation. We investigated the predictive value of age of psychosis onset for severity, functioning and demographic variation by: 1) comparing groups based on traditional cut-offs for age of psychosis onset, and 2) using receiver operating characteristic (ROC)-curve calculations, without a priori age of onset cut-offs.
Method: Participants were 88 (45 female, 43 male) children and adolescents with a recent onset of psychosis (age range = 6.7–17.5 years; $M = 13.74$, $SD = 2.37$).
Results: The VEOP group had significantly shorter duration of untreated illness and untreated psychosis, and lower functioning than the EOP group. The VEOP and EOP groups did not differ significantly on gender proportion, urbanicity, psychotic diagnosis, family history of psychotic disorder, psychotic, depressive and anxiety symptoms or IQ. When applying ROC-curves to the lowest three quartiles of positive psychotic symptoms scores, the optimal age-cut-off was 14.0 years (sensitivity = 0.62; specificity = 0.75). For the highest quartile of functioning scores, the optimal differentiating cut-off for age of psychosis onset was 14.7 years (sensitivity = 0.71; specificity = 0.70).
Conclusions: Larger samples of patients, assessed at presentation and followed-up, are necessary to clearly examine clinical presentation and outcome as a function of social and neural development to better understand if the differentiation between VEOP and EOP is justified. This will aid the development of predictive diagnostic tools, more accurate prognosis prediction, and age-tailored therapeutic interventions.

1. Introduction

Schizophrenia is a heterogeneous clinical syndrome of unknown aetiology, comprising a number of psychopathological domains and patients vary considerably in which pathologies are manifest (Insel, 2010). In accordance with this definition, symptoms of schizophrenia are heterogeneous, even within the same age group (Carpenter and Buchanan, 1989). Besides the heterogeneity of the clinical presentation, some differences related to the age of onset (i.e. premorbid abnormalities, longer duration of untreated psychosis [DUP], poorer outcome) have been highlighted (Armando et al., 2015). Consequently, the need of age-specific research in the area of psychosocial treatments for children and adolescents with schizophrenia has been argued (Tiffin and Welsh, 2013).

In accordance with this evidence, a distinction has traditionally been made between adult-onset psychosis (AOP; ≥18 years of age) and early onset psychosis (EOP; onset <18 years of age), which occurs in approximately one-third of all patients diagnosed with a psychotic disorder (Madaan et al., 2008). While this cut-off is arbitrary, there is evidence that psychotic illness which begins before the age of 18 tends to be more severe than AOP (Rabinowitz et al., 2006; Reichert et al., 2008; Kumra and Schulz, 2008; Díaz-Caneja et al., 2015). Compared to AOP, EOP is more strongly associated with premorbid social impairments, DUP (Hollis, 2003; Schimmelmann et al., 2007), a more severe clinical course (Werry et al., 1991; Eggers and Bunk, 1997), more severe premorbid neurodevelopmental abnormalities (Vourdas et al., 2003), greater genetic loading (Kumra and Schulz, 2008), and more severe negative symptoms (Pencer et al., 2005; Kao and Liu, 2010).

* Corresponding author at: Children Hospital Bambino Gesù, Piazza Sant'Onofrio 4, 00165 Rome, Italy.
E-mail address: marco.armando@opbg.net (M. Armando).

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While the differences between AOP and EOP are well supported, there is still debate regarding whether EOP should be considered as a homogeneous entity. Most commonly, the cut-off of psychosis onset at or before 12 years of age is used; that is, EOP with onset between 13 and 17 years of age (sometimes referred to as adolescent onset psychosis) and very early onset psychoses (VEOP), with onset of illness at age 12 years or younger (often referred to as childhood onset schizophrenia). While many studies have investigated the clinical and neurocognitive features of VEOP specifically (see Kyriakopoulos and Frangou, 2007 for a review), very few have directly compared the clinical characteristics of EOP and VEOP. Those that have demonstrate the long-term outcome of individuals with VEOP appears to be worse than EOP. These individuals do more poorly at school and are less likely to have been employed than individuals with EOP (Biswas et al., 2006). They have a longer first hospital admission and subsequently have a greater number of days in hospital each year (Rabinowitz et al., 2006). There is also meta-analytic evidence that anti-psychotic medication initiated at a younger age is associated with an increased risk of side effects, particularly weight gain, higher discontinuation rates and leaving school early (Stafford et al., 2015). Evidence of neurocognitive variations according to age of psychosis onset is variable. Biswas and colleagues (Biswas et al., 2006) showed poorer cognitive function, namely IQ, memory and perceptuomotor skills, in individuals with VEOP compared to EOP. Conversely, Rhinewine et al. (2005) found no significant differences in the neurocognitive performance of VEOP and EOP groups, and no significant association between cognitive ability and age of psychosis onset.

In summary, there is still a lack of evidence of an 'age of psychosis onset effect' in youth <18 years of age. We lack the knowledge to determine whether psychoses with an onset before 18 years of age should be differentiated into VEOP and EOP, and if so, whether the traditional age cut-offs are clinically valid. A better understanding of this is important for the development of diagnostic criteria and age-specific therapeutic strategies. Indeed, the urgent need for studies investigating the role played by age of onset of psychosis on clinical presentation and response to therapeutic interventions has recently been highlighted (Schimmelmann and Schultze-Lutter, 2012; Schimmelmann et al., 2013; NICE, 2013).

To our knowledge, no study has investigated the clinical and demographic differences between young people with VEOP and EOP *at the time of psychosis onset*. In the current study, we examined psychoses with onset before the age of 18 years by: 1) examining differences at presentation between individuals with EOP and VEOP according to the traditional cut-offs for age of psychosis onset; and 2) by using receiver operating characteristic (ROC)-curves to determine if there was a clinically significant cut-off for the age of psychosis onset in the current sample.

2. Methods

2.1. Participants and procedure

Participants in this study were 88 (45 female, 43 male) children and adolescents consecutively admitted to the Child and Adolescent Neuropsychiatry Unit of the Clinical and Research Hospital Bambino Gesù of Rome with a recent onset of psychosis between 2012 and 2014. Patients had psychosis onset between ages 6.7 and 17.5 years ($M = 13.74$, $SD = 2.37$, median = 14.1) and had no previous drug treatment for psychosis (typical/atypical antipsychotics). Specific psychotic diagnoses are listed in Table 1. Exclusion criteria were past diagnosis of psychotic disorder, traumatic brain injury or known neurological disorder, verbal IQ < 70, and current drug or alcohol abuse. The participation rate was 95% of the consecutively admitted children/adolescents. Four patients (5%) were excluded because of the presence of an exclusion criteria (three due to verbal IQ < 70, one due to drug abuse). No eligible patient refused to participate. The study was approved by the Ethics Committee of the Clinical and Research Hospital Bambino Gesù of Rome. Participants gave written informed assent and written informed consent was given by their parents/legal guardian.

2.2. Measures

Mental disorders were assessed using the Schedule for Affective Disorders and Schizophrenia for School Aged Children Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). Psychotic symptoms were indexed on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). This 30-item scale is used to assess the severity of positive and negative symptoms of psychosis, as well as general psychopathology. Both interviews were administered to the participants and their parent/guardian. All participants were screened for autism-spectrum disorder using the Autism Quotient Child (Auyeung et al., 2008) or Adolescent (Baron-Cohen et al., 2006) versions, completed by participants and their parent/guardian. In the case of positive screening, participants were assessed by a trained clinician on the Autism Diagnostic Observation Schedule-Generic (Lord et al., 2000). None met criteria for autism-spectrum disorder. Participants completed (via self-reported) the Multidimensional Anxiety Scale for Children (MASC) (March et al., 1997) to obtain an index of the severity of anxiety symptoms and the Children's Depression Inventory (CDI) (Kovacs, 1988) to obtain a global rating of depressive symptoms. Functioning was measured with the Childhood Global Assessment Scale (CGAS) (Shaffer et al., 1983). IQ was assessed with the Wechsler Intelligence Scale for Children (WISC-III) (Wechsler, 1991).

Duration of untreated illness (DUI) was defined as the delay between the onset of the first psychiatric disorder and the onset of criteria treatment, following the methodology used by Keshavan et al. (2003) DUP was defined as the delay between the onset of psychosis and the onset of criteria treatment, following the methodology used by Larsen et al. (2001).

We documented any first-degree relative with psychosis. Nine participants had no available information on family history (eight due to adoption). Living in an urban environment within the last three years was categorized according to a population of ≤100,000 or >100,001 (based on Dragt et al., 2011). Socio-demographic information were obtained from parents/guardians.

2.3. Statistical analyses

First, we divided and compared groups based on traditional cut-offs for age of psychosis onset: VEOP (onset of psychosis ≤ 12 years of age) and EOP (onset of psychosis 13–17 years of age). For group comparisons on categorical data, Chi-square was used. Independent Samples Mann–Whitney U was employed for group comparisons of continuous data. Effect sizes were calculated with Cohen's d for continuous variables and Cramer's phi for categorical data.

To investigate the predictive value of age of onset for psychotic symptom severity and functioning, without using the a priori cut-offs between EOP and VEOP, ROC-curves were calculated. Traditionally, ROC-curves are used to evaluate the ability of a test to detect a golden standard disorder/abnormality. Here, the curves were used in a slightly different context to evaluate the prognostic ability of age of onset at different age cut-offs. Thus, instead of evaluating whether, based on an a priori cut-off value, a test-score predicted an outcome with sufficient sensitivity (SENS) and/or specificity (SPEC), here optimal prediction of the outcome was used as a criterion to select the diagnostically most relevant age of onset cut-off. This approach was chosen because: (1) it allowed for the identification of an optimal age of onset cut-off (age with optimal SENS/SPEC), and; (2) it provided insight into the general prognostic value of age of onset for poor outcome.

In order to identify the factors associated with the poorest functioning and most severe symptoms using ROC analyses, the highest 25% of PANSS scores were compared to the lowest 75% of PANSS scores