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Can age at sexual maturity act as a predictive biomarker for prodromal negative symptoms?

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ABSTRACT

Background: Puberty and reproductive hormones have been identified as having a potential role in schizophrenia. Earlier reports have suggested associations between later age at puberty and schizophrenia in males. Similarly, associations have been reported between testosterone levels and psychotic symptoms. In this report, we examined the association between age at puberty and prodromal symptoms of psychosis.
Methods: 58 child or adolescent family members of individuals with schizophrenia were interviewed using the Scale of Prodromal Symptoms and the Tanner Maturational Scale. Age at Tanner pubertal stage was determined and regression analyses were used to explore associations between prodromal symptoms and age at puberty.
Results: Among males, delayed age at puberty was associated with greater severity of prodromal symptoms; the association between negative prodromal symptoms and delayed age was significant ($p = 0.001$). In females, the association was not statistically significant.
Conclusions: Our results suggest that delayed age at puberty may be associated with negative prodromal symptoms of schizophrenia in males. Our findings suggest that delayed age at puberty could potentially be a predictive biomarker for psychopathology in males at risk for schizophrenia.

1. Introduction

The search for early markers of psychosis has been a long and elusive process. A number of putative clinical and biological markers have been implicated including neurological soft signs (Heinrichs and Buchanan, 1988; Smith et al., 1999; Chan et al., 2010), abnormal eye movements (Campion et al., 1992; Lee and Williams, 2000), cortical gyrification patterns (Palaniyappan and Liddle, 2012) and more recently mismatch negativity (Nagai et al., 2013). However, there is still a need to identify methods of predicting psychosis. One suggested clinical biomarker relates to the role of reproductive hormones and age at puberty. Saugstad (1989) commented on the potential link between age at puberty and psychotic illnesses. She stated that early maturing females are more prone to developing affective psychosis while late maturing males are more prone to developing schizophrenia. Further, she hypothesized that these differences could be secondary to an altered rate of elimination of synapses in early maturing females and reduced synaptic density in the late maturing males. Cohen et al. (1999) noted that earlier age at puberty was associated with later age of onset of schizophrenia in women; in men, however, this association was in the opposite direction. Gruzelier and Kaiser (1996) noted that both males and females with extreme variations in age at onset of puberty scored higher on various schizotypy measures, including unreality, social withdrawal and anhedonia.

Puberty is associated with a pulsatile release in gonadotrophin releasing hormone (GnRH), leutinizing hormone (LH), androgens and estrogen (Veldhuis, 1996); both androgens and estrogen have been identified as being neuroprotective (Bialek et al., 2004; Markham, 2012). Thus, delayed puberty and delayed exposure of brain matter to the reproductive hormones can adversely affect critical brain processes during puberty. The role of neurosteroids, including testosterone, DHEA and estrogen in schizophrenia has been examined in depth. Estrogen has been identified as a potential explanation for the delayed onset of psychosis in women and the premenstrual exacerbations of psychotic symptoms (Kendell et al., 1987; Mahe and Dumaine, 2001; Bergemann et al., 2002). The association between testosterone levels and chronic schizophrenia (Markham, 2012) in males has, however, been controversial with some authors reporting a positive association between low testosterone and chronic schizophrenia and others being unable to confirm the association. Besides chronic schizophrenia, studies have examined testosterone levels in individuals at high risk (HR) of developing psychosis (Van Rijn et al., 2011) and first episode

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psychosis (FEP) (Huber et al., 2005; Ceskova et al., 2007) with varied results. Van Rijn et al. (2011) and Huber et al. (2005) noted lower testosterone levels in their groups of HR and FEP participants, while Ceskova et al. (2007) were unable to confirm the association. However, most authors agree that these differences appear to be driven by negative symptoms (Markham, 2012). In an earlier paper, Keshavan and Hogarty (1999) proposed that delayed exposure to testosterone may affect the naturally tuned pruning of glutamatergic pyramidal neurons in the cortex and association areas. Studies of young relatives at high risk for psychosis can potentially shed light on this important issue.

In this study, we aimed to examine the following hypotheses: 1. Delayed age at onset of puberty will be associated with greater prodromal symptoms of psychosis in males. 2: An earlier age of onset of puberty will be associated with greater prodromal symptoms in females. We examined these hypotheses in a group of child or adolescent relatives assessed as part of a longitudinal study of familial high risk subjects.

2. Method

2.1. Participants

58 family members (29 males and 29 females) of individuals with schizophrenia and schizoaffective disorder living in the Pittsburgh, PA area were included in this study. Among the 58 family members, 46 were offsprings, 4 were siblings and 8 were second degree relatives. The diagnosis in the index individual was confirmed using the Structured Clinical Interview for DSM-IV Disorders (SCID) (First et al., 2002). The participants in this study were part of a larger sample that has been discussed in detail in a previous paper (Keshavan et al., 2004). Approval for the study was obtained from the Institutional Review Board of the University of Pittsburgh. A written and informed consent was obtained from the participants and/or their guardian for minors.

2.2. Materials

All participants underwent a series of evaluations including the Structured Interview for Prodromal Syndromes (SIPS) and rated with the Scale of Prodromal Symptoms (SOPS) for the presence of one or more prodromal symptoms (Miller et al., 2002). IQ was assessed using standard IQ assessments including the Revised Wechsler Adult Intelligence Scale (Wechsler, 1981) and the Wechsler's Abbreviated Scale for Intelligence (Wechsler, 1999). The Tanner Maturational Scale (Marshall and Tanner, 1969, 1970) was employed to assess sexual maturity. This assessment was done by self-report. The Tanner Maturational Scale (TMS) is a scale of 5 progressive stages of phenotypic pubertal development (breast and pubic hair in females and genital and pubic hair in males). Based on the development of secondary sexual characteristics, individuals were grouped into 9 Tanner stages as stage 1 — prepubertal, stage 2 — onset of puberty, and so on through to stage 5 — adult (1 to 5 in steps of 0.5 increments). Table 1 provides details about the distribution of age across the various Tanner stages.

Table 1
Distribution of Tannerstage and average age in years in the sample.

Tannerstage	Average age in years (sample std. dev)
1	10.94 (1.67)
1.5	11.19 (2.02)
2	12.30 (1.37)
2.5	13.11 (2.05)
3	13.75 (2.13)
3.5	14.91 (2.04)
4	14.75 (2.38)
4.5	15.58 (2.15)
5	17.41 (2.03)

2.3. Data analysis

The participants were first divided into two categories — "Late maturers" and "Others" based on the age at Tanner stage. In particular, for each Tanner stage, the mean and standard deviation of age was computed. An individual was defined to be a "Late maturer" if their age was more than one standard deviation above the mean for the HR group at that Tanner stage (henceforth called "Latematurer"). A new variable "Maturity" was created by subtracting the mean age for that Tanner stage from the age of that individual and dividing by the standard deviation of age for that Tanner stage. As before, the mean and standard deviation were computed for each Tanner stage. These two variables were subsequently entered as predictor variables in separate negative binomial regressions. The following dependent variables were examined: SOPS (total score, and the subscales including positive, negative, disorganized and general scores). Negative binomial regression was used since the dependent variables took only integer values. Negative binomial regressions were preferred over Poisson regressions due to over-dispersion (i.e., the conditional variance was higher than the conditional mean). Likelihood ratio tests comparing the negative binomial models to Poisson models were always significant indicating the presence of over-dispersion. These regressions were covaried for age, gender and race. The regression analyses were carried out with the entire sample, and repeated using single-gender subsamples. All analysis was carried out using STATA SE 13 (StataCorp, 2013).

3. Results

3.1. Sample characteristics

The mean age of the sample was 13.72 years (SD = 2.44; range:10–18 years) with no significant difference between the genders ($p = 0.20$). The SOPS scores among the participants ranged from 0 to 47 with 20 participants scoring 0 on the SOPS. The two genders did not differ significantly on SOPS scores — total ($p = 0.89$), positive symptoms ($p = 0.32$); negative symptoms ($p = 0.95$); disorganized symptoms ($p = 0.61$), and general symptoms ($p = 0.27$), and IQ ($p = 0.93$). Similarly, the average of the Latematurer indicator variable ($p = 0.72$) and maturity ($p = 0.89$) were not significantly different between the two genders.

3.2. Regression using Latematurer and Maturity

Negative binomial regressions using the Latematurer (+1 SD or ~1.5 yrs/18 months) and the maturity variable as predictor variables (in separate regressions) did not reveal any significant coefficients on any of the SOPS total or subscale scores (p value > 0.05). However, when the same regressions were carried out separately among the two genders, the coefficients for males were positive on SOPS total and all the subscale scores while those for females were always negative. Controlling for age and race, there was a statistically significant association between SOPS negative symptoms in males and a delayed age of puberty; Latematurers were more likely to have negative symptoms (p-value = 0.001) as compared to early maturers (Table 2). This association remained significant after correcting for multiple comparisons, with the p-value (0.001) below the Bonferroni corrected threshold for five comparisons (0.010 at $\alpha = 0.05$). These results hold after controlling for IQ in addition to the other covariates (coefficient = 2.09, p-value = 0.001). A similar association was noted when the analysis was carried out using the maturity variable as the explanatory variable (coefficient = 0.87, p-value = 0.006), and age and race as covariates. As before, the p-value is below the Bonferroni corrected threshold for five comparisons (0.010). Fig. 1 illustrates this graphically. The figure plots the predicted values from two negative binomial regressions of SOPS (NS) on maturity, one each for males and females. As can be seen from the figure, the SOPS (NS) scores are largely