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Can Age at Sexual Maturity act as a Predictive Biomarker for prodromal negative symptoms?

Seethalakshmi Ramanathan^{1,2}, Jean Miewald³, Debra Montrose³, and Matcheri S Keshavan^{3,4,5}

¹Hutchings Psychiatric Center, Syracuse, NY

²SUNY Upstate Medical University, Syracuse, NY-13210

³Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA

⁴Beth Israel Deaconess Medical Center, Boston, MA

⁵Department of Psychiatry, Harvard Medical School, Boston, MA

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 Maturation 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.

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Corresponding author: Matcheri S Keshavan, mkeshava@bidmc.harvard.edu.

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Contributors:

MSK designed the study.

JM, and DM extracted the data from the charts and files

SR did the statistical analysis, literature search and wrote the first draft of the paper.

All authors have read and approved of the final draft of the paper.

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.

Keywords

puberty; tanner stage; psychosis; negative symptoms; biomarker

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 (Chan, Xu, Heinrichs, Yu, & Wang, 2010; Heinrichs & Buchanan, 1988; Smith, Hussain, Chowdhury, & Stearns, 1999), abnormal eye movements (Campion et al., 1992; Lee & Williams, 2000), cortical gyrification patterns (Palaniyappan & 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 (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 (Cohen, Seeman, Gotowiec, & Kopala, 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 (Gruzelier & 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 has been associated with changes in mood and behaviors. 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, Zaremba, Borowicz, & Czuczwar, 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 (Bergemann et al., 2002; Kendell, Chalmers, & Platz, 1987; Mahe & Dumaine, 2001). 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 psychosis (FEP) (Ceskova, Prikryl, & Kasperek, 2007; Huber, Tettenborn, Leifke,

& Emrich, 2005) with varied results. Van Rijn et al (Van Rijn et al., 2011) and Huber et al (Huber et al., 2005) noted lower testosterone levels in their groups of HR and FEP participants, while Ceskova et al (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 (Keshavan & 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, Spitzer, Gibbon, & Williams, 2002). The participants in this study were part of a larger sample that has been discussed in detail in a previous paper (Keshavan, Diwadkar, Montrose, Stanley, & Pettegrew, 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 Revised Wechsler Adult Intelligence Scale (Wechsler, 1981) and the Wechsler's Abbreviated Scale of Intelligence (Wechsler, 1999). The Tanner Maturation Scale (Marshall & Tanner, 1969; Marshall & Tanner, 1970) was employed to assess sexual maturity. This assessment was done by self-report. The Tanner Maturation 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 I provides details about the distribution of age across the various Tanner stages.

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 > 0.5). 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 II). 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). Figure I 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 unaffected by maturity for females. In contrast, for males, there is a sharp increase in the scores with an increase in maturity. As with the Latematurer variable, including IQ as a covariate did not qualitatively affect the results (coefficient = 0.83, p-value = 0.011).

4. Discussion

Our study suggests that among males considered to be at a familial high risk of developing schizophrenia, delayed onset of puberty is associated with elevated negative prodromal symptoms. Among females, on the other hand, no significant association was noted. However the trend was in the hypothesized directions, i.e., early maturing females were likely to have greater prodromal symptoms. Further, no association was noted between age at puberty and the other categories of prodromal symptoms, including positive, general and disorganization or with the indices of psychosis proneness.

Puberty is associated with a number of changes in the brain, including elimination of synapses and/or other neural elements (pruning), and development of brain connectivity. Animal studies have noted a reduction in the volume of the visual cortex in female rats (Nuñez, Lauschke, & Juraska, 2001) and pruning in the medial amygdala in hamsters (Zehr, Todd, Schulz, McCarthy, & Sisk, 2006) during puberty. In humans, puberty has been associated with changes in gray matter volume (Neufang et al., 2009), density (J. S. Peper et al., 2009), thickness (Raznahan et al., 2010) and white matter development (Ladouceur, 2012; J. Peper, Hulshoff Pol, Crone, & Van Honk, 2011). These changes may be triggered by the dramatic increase in androgenic steroids including testosterone and estrogen. For example, estrogen has been shown to increase the density of synapses in rat hippocampus (Desmond & Levy, 1997), while testosterone may increase synaptic elimination in rats (Jordan, Watamura, & Arnold, 1995). Similarly, human studies have noted associations between testosterone levels in boys and increases in white matter volume (Perrin et al., 2008) and global gray matter volumes (J. S. Peper et al., 2009). Further, levels of Luteinizing Hormone (LH), which also increases during puberty, has been associated with regulating gray (Raznahan et al., 2010) and white matter development (Perrin et al., 2008). Gonadal steroids may affect gene expression and thus influence the maturational processes that occur during puberty (Keshavan & Hogarty, 1999). This effect may occur through the androgen receptor system, which has been noted to be in abundance in the frontal cortex and the medial temporal lobe. The androgen receptor system can, in turn, influence the dopaminergic and glutamatergic systems (Aubele & Kritzer, 2012). We can speculate that delayed puberty in males, could have affected the natural longitudinal trajectories of cortical development in these individuals, leading to the observed association.

It is possible that the association between negative symptoms and puberty was driven by the relationship between the events at puberty in males and maturation of the frontal lobes. This

hypothesis is reinforced by the developmental trajectories of the various regions of the brain; gray matter in the frontal and parietal lobes have been noted to peak a little later in males (12 years) as compared to females (10 years) (Paus, 2005), subsequent to which they undergo pruning. While the triggers and mechanisms behind pruning are yet unknown, we can speculate that if testosterone was one of the triggers or mechanisms involved in pruning (Blanton et al., 2004; Jordan et al., 1995), it would influence reorganization of the frontal lobe (e.g. altered timing of pruning), which, in turn, could drive the association between negative symptoms and delayed onset of puberty. This relationship between frontal lobe development and gender may also be driving our second observation pertaining to the differential findings between the two genders. Blanton et al (Blanton et al., 2004) point to the potential influence of pubertal hormones on the development of the frontal cortex in boys but not in girls. Thus, it is possible that puberty and the steroidal hormones do not have a significant influence on the prodromal symptoms in females, due to the lack of influence on frontal lobes. Epidemiological studies provide credence to our observations about the putative influence of puberty on negative symptoms in males. Age at onset of psychotic symptoms is later in women as compared to men; age at onset of psychotic symptoms is around 15–25 years in men (Faraone, Chen, Goldstein, & Tsuang, 1994; Jablensky et al., 1992). Additionally, some studies have noted a higher prevalence of negative symptoms in men as compared to females (Gur, Petty, Turetsky, & Gur, 1996; Mueser, Bellack, Morrison, & Wade, 1990). However, we cannot rule out the possibility that besides pubertal hormones, unexplored or unexamined differences in early life/ developmental factors between the genders may have acted as confounding factors obscuring any true association in females. One such category of environmental factors that influences puberty but not prodromal symptoms, includes body mass index and leptin levels, which trigger the onset of puberty (Ahima, Dushay, Flier, Prabakaran, & Flier, 1997). Finally, it is possible that with the limited number of participants, our study did not have sufficient power to capture an association between age at onset of puberty and prodromal symptoms in females.

A number of theories have been proposed regarding the pathogenesis of schizophrenia; including the “two-hit” hypothesis that proposes that brain maturational derailment interacting with environmental stress (second hit) during adolescence on a vulnerable brain (first hit) can trigger psychosis (Keshavan & Hogarty, 1999). Our findings may suggest that one factor underlying the second hit could be delayed release of neurosteroids; which in turn hints at a potential etiopathogenic role for the neurosteroids in psychosis. On the other hand, delayed release of neurosteroids could also be secondary to the “second hit” or environmental stress affecting the hypothalamo-pituitary-gonadotrophin axis; suggesting that our finding could be indicative of the stress. Grumbach (Grumbach, 2002) notes that in rhesus monkeys, puberty is triggered by changes in the levels of GABA and NMDA activity. This in turn implies that dysfunction in GABA and NMDA activity could have resulted in both delay in puberty and prodromal symptoms. In either case, the finding that delayed puberty may be associated with negative symptoms in males suggests that age at puberty could be a potential clinical marker. It also reinforces some of the existing work of the role of testosterone in individuals with schizophrenia.

Conclusion

Summarizing, our study explores the relationship between age at puberty and prodromal symptoms of psychosis and establishes an association between delay in age at puberty and negative prodromal symptoms among males. The study is limited in that it does not explore the reasons behind the observed association. Further, because of the limited number of converters to psychosis, we had to restrict our analysis to individuals with prodromal symptoms and were unable to confirm the relationship in individuals who converted to psychosis. Finally, we used TMS to determine age at puberty. Although fairly reliable (Slora et al., 2009), TMS can be subjective in nature. Further, the self-reporting nature of the assessment could have led to reporting bias. Nonetheless, our findings suggest that age at puberty can serve as a potential clinical neuroendocrine marker of psychosis. Our study also raises a number of potential questions for future research including the role of the hypothalamic-pituitary-gonadal (HPG) axis and reproductive hormones in psychosis.

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Figure I.

Predicted values from two negative binomial regressions of SOPS (NS) on maturity, males (Left panel) and females (Right panel). Hollow circles refer to the actual relationship between TMS and SOPS (NS) while the solid circles refer to the best predicted fit using negative binomial regressions.

Table I

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)

Negative binomial regression using Latematurer (+1 SD or ~1.5 yrs/18 months) variable as the predictor and the SOPS scores as dependent variables

Table I

	Total (N=58)		Males (N=29)		Females (N=29)	
	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value
TOTAL	-.019	0.98	1.22	0.09	-1.99	0.16
PS	-.49	0.55	0.57	0.43	-2.63	0.17
NS	.549	0.50	2.08	0.001 *	-2.20	0.12
DS	-.57	0.61	0.53	0.64	-16.76	0.99
GS	-.19	0.61	0.46	0.75	-1.05	0.42

(*)p<0.05