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Timing of Prenatal Stressors and Autism

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Recent evidence supports a role for genetics in autism, but other findings are difficult to reconcile with a purely genetic cause. Pathological changes in the cerebellum in autism are thought to correspond to an event before 30–32 weeks gestation. Our purpose was to determine whether there is an increased incidence of stressors in autism before this time period. Surveys regarding incidence and timing of prenatal stressors were distributed to specialized schools and clinics for autism and Down syndrome, and to mothers of children without neurodevelopmental diagnoses in walk-in clinics. Incidence of stressors during each 4-week block of pregnancy was recorded. Incidence of stressors in the blocks prior to and including the predicted time period (21–32 weeks gestation) in each group of surveys was compared to the other prenatal blocks. A higher incidence of prenatal stressors was found in autism at 21–32 weeks gestation, with a peak at 25–28 weeks. This does support the possibility of prenatal stressors as a potential contributor to autism, with the timing of stressors consistent with the embryological age suggested by neuroanatomical findings seen in the cerebellum in autism. Future prospective studies would be needed to confirm this finding.

KEY WORDS: Autism; prenatal; stress; development.

INTRODUCTION

Evidence demonstrating the role of genetic factors in the etiology of autism has accumulated over recent years (Folstein & Rutter, 1977; Maestrini, Paul, Monaco, & Bailey, 2000; Ritvo, Freeman, Mason-Brothers, Mo, & Ritvo, 1985; Trottier, Srivastava, & Walker, 1999). Studies show a higher concordance rate of autism among monozygotic than dizygotic twins, and a higher rate among siblings than in the general population (Folstein & Rutter, 1977; Ritvo *et al.*, 1985; Steffenburg, Gillberg, Hellgren, Jakobsson, & Bohman, 1989; Trottier *et al.*, 1999). However, some monozygotic twins have also been found to be discordant for autism (Folstein & Rutter, 1977; Kates *et al.*, 1998; Ritvo *et al.*, 1985; Steffenburg *et al.*, 1989), and the causative role of a number of environmental factors has been considered (Burd, Severud, Kerbeshian, & Klug, 1999).

Standardized interviews conducted with a large sample of mothers of autistic children revealed a higher incidence of minor obstetric complications compared to that among control samples, but this was thought to be secondary to increased familial risk (Zwaigenbaum *et al.*, 2002). This finding could also be attributed to a response bias. A retrospective study of a prospectively collected database provided evidence

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for a number of perinatal risk factors associated with autism including maternal cigarette smoking in early pregnancy, being small for gestational age, congenital malformations, being born outside Europe and North America, cesarean delivery, and a 5-min Apgar score below 7 (Hultman, Sparén, & Cnattingius, 2002). Other studies suggested that insults during prenatal development, such as exposure to thalidomide (Stromland, Nordin, Miller, Åkerström, & Gillberg, 1994), valproate (Williams *et al*., 2001), or cocaine (Davis *et al*., 1992), might lead to autism. Furthermore, in dizygotic twins discordant for autism, the autistic twin is more likely to have experienced more perinatal stress (hemolytic disease, foot presentation, face presentation, or asphyxia) (Steffenburg *et al*., 1989). Season of birth has also been implicated in some studies, with evidence for an increased incidence of March birthdays among children with autism (Gillberg, 1990; Mouridsen, Nielsen, Rich, & Isages, 1994). These findings do raise the possibility that the etiology of autism may not be purely genetic, and environmental factors must be further considered.

Psychological stress during pregnancy has been recognized as a possible risk factor for adverse physical, psychological, behavioral, and developmental outcomes in humans (Dawson, Ashman, & Carver, 2000). Development of the early personality of the child (Niederhofer & Reiter, 2000), schizophrenia (Van Os & Selten, 1998), and emotional disturbances (Ward, 1991) have also been found to be affected by maternal stress. Mothers of children with autism have reported significantly higher family discord and psychiatric problems during their pregnancies than mothers of nonautistic children (Ward, 1990). Research with animal models has also identified a link between maternal stress and a range of adverse behavioral outcomes for the offspring such as abnormal responses to fearful stimuli once the animals reach adulthood (Ward, Johnson, Salm, & Birkle, 2000; Weinstock, 1997). Maternal stress in animals also results in changes in the hypothalamic–pituitary–adrenal axis (HPA) and changes in the amygdala, including expansion of the lateral nucleus, that last into adulthood in the offspring (Ward, *et al*, 2000; Salm *et al*., 2004). The cerebellum has not been investigated in this manner. However, the risk of damage to cerebellar granule cells is increased in rats after prenatal exposure to glucocorticoids (Ahlbom, Gogvadze, Chen, Celsi, & Ceccatelli, 2000), which are part of the stress response.

Neuroanatomical research has revealed increased neuronal packing density in the amygdala in autism (Bauman & Kemper, 1994). Decreased dendritic arborization and increased neuronal cell-packing density in the hippocampus is also seen (Bauman & Kemper, 1994). MRI studies have shown decreased amygdalar and hippocampal volume in adolescents and adults with autism when adjusted for total brain volume (Aylward *et al*., 1999), but in young children with severe autism, volume of the amygdala is increased and the hippocampus is normal when covaried for total brain volume (Sparks *et al*., 2002). Abnormalities have also been reported in the cerebellum (Courchesne, Townsend, & Saitoh, 1999). Pathologically, the cerebellum demonstrates a decrease in Purkinje cells in the cerebellar hemispheres, and abnormalities are seen in the fastigeal, emboliform, and globose nuclei in autism (Bauman & Kemper, 1994). Lesion studies suggest potential roles these various pathological findings might play in autism. Surgical resection of the hippocampus and amygdala in neonatal monkeys has been shown to result in behaviors commonly seen in autism such as gross motor stereotypies, tantrums in novel situations, poor eye contact, and limited facial expression (Bachevalier, 1991). In humans the amygdala has been strongly associated with processing of information regarding fearful stimuli, and deficits in the perception of emotional expressions, particularly fear, have been demonstrated in patients with amygdalar damage (LeDoux, 2000). Lesion studies have shown that the cerebellum may play a role in emotion, behavior, learning, and possibly language (Schmahmann, 1994).

Many consider the structural abnormalities in the autistic brain consistent with a failure in maturation (Bauman & Kemper, 1994). Whereas less is known about human amygdalar development, given what is known about the timing of the tight developmental relationship between the olivary climbing fibers and the Purkinje cells (Fleischig, 1920; Rakic, 1971; Rakic & Sidman, 1970; Yakovlev & Lecours, 1967), the preservation of olivary neurons in the presence of markedly reduced numbers of Purkinje cells in autism suggests that the onset of the cause of these findings would occur at or before approximately 30 weeks of gestation (Bauman & Kemper, 1994). Others have suggested a cause at or before 32 weeks gestation (Bailey *et al*., 1998).

Research in animal models has utilized various methods to induce maternal stress, but the severity of the maternal stressor and the point during gestation at which the stressor occurs are particularly significant (Weinstock, 1997). Examination of animal models of prenatal stressors focused at the time analogous to

those proposed for autism has not yet been done. The purpose of our research was to survey a population of parents of autistic children as well as parents of children without neurodevelopmental diagnoses and children with Down syndrome, and compare the incidence and timing of prenatal stressors during these pregnancies. The impact of the severity of stressors was also examined. Whereas earlier studies have shown an increased incidence of prenatal stressors in autism, some of these findings could be attributed to a response bias. However, due to the developmental abnormalities reported in the cerebellum in autism, we predicted an increased incidence in stressors prior to the gestational time period predicted as above, which would not be readily attributable to a response bias. Therefore, we hypothesized that there would be an increased incidence of stressors prior to 30–32 weeks gestation in autism.

METHODS

Participants

Surveys were handed out or mailed with an explanatory cover letter and return postage to specialized schools and clinics for autism and Down syndrome, and to walk-in clinics to gather information from mothers of children without neurodevelopmental diagnoses. The cover letters were identical for all groups, except that the physicians signing the letters varied with the clinic sampled. The cover letters stated that we were "investigating the relationship between problems around the time of pregnancy and developmental disabilities." Specific diagnoses such as Down syndrome and autism were not mentioned in the cover letter. Four hundred and thirty-four surveys to mothers of children with autism were distributed in the clinics of Dartmouth-Hitchcock Medical Center (99 surveys), the Boston-Higashi School (114 surveys), the Cambridge-Ladders Clinic (196 surveys), and in Boston area autism support meetings (25 surveys). One hundred and ninety-one surveys to mothers of children with Down Syndrome were distributed in the Dartmouth-Hitchcock Medical Center clinic. Five hundred and seventeen surveys to mothers of children without neurodevelopmental diagnoses were distributed in the Dartmouth-Hitchcock Medical Center walk-in clinic (417 surveys) and the Dartmouth-Hitchcock Medical Center Buck Road clinic (100 surveys) as control surveys. Individuals with autism had been diagnosed according to DSM-IV criteria (American Psychological Association, 1995). Children without neurodevelopmental diagnoses, as confirmed by a history from the parents, were selected as a control group. Children with Down syndrome, as confirmed by karyotype, were selected as a second control group to control for the possibility that the presence of a neurodevelopmental diagnosis which would not be influenced by prenatal stressors might result in increased positive reports on survey responses.

PROCEDURES

Survey questions gathered information on the child's birthdate, whether the child was born early or late, how many weeks early or late the child was born, and whether any major stressful events occurred during or within 1 year after pregnancy, the onset and the end of when these occurred, and what was the event. Questions were also asked concerning maternal prenatal medical illness and prenatal medications and immunizations, when they occurred, and what they were. Questions regarding the child's current language ability were also included. Events that matched major life events in the Social Readjustment Rating Scale (SRRS) (Holmes & Rahe, 1967) were *a priori* tabulated in 4-week blocks by the investigators spanning the duration of pregnancy, and were also tabulated during the first 4-week block after delivery, with gestational age derived from the birthdate and survey responses to how many weeks early or late was the delivery. Incidence of stressors were then compared between groups as well as across the 4-week blocks within each group. To adjust for stressor severity, a similar comparison was performed after each stressor was multiplied by severity scores according to the SRRS (examples: spouse's death – 100, divorce – 73, close family member's death – 63, fired at work – 47, change in health of close family member – 43) (Holmes & Rahe, 1967). The rank order and scoring of these stressors has been shown to be homogeneous among subjects in the United States (Masuda & Holmes, 1967). Furthermore, recall of these stressors has been shown to be stable over time (Casey, Masuda, & Holmes, 1967). We predicted that the 4-week blocks including and preceding the 29–32 week block would reveal an increased incidence of stressors in autism, since this includes the dates predicted as described

above (Bailey *et al.*, 1998; Bauman & Kemper, 1994). Procedures followed were in accordance with the ethical standards of Massachusetts General Hospital and Dartmouth-Hitchcock Medical Center.

The primary index comparison was a χ^2 analysis to determine, for each group, whether the 4-week blocks including and preceeding the 29–32 week block would reveal an increased incidence of stressors as compared to the other blocks. The individual 4-week blocks were also assessed for whether they were outside the quatratic fit of the other blocks of perinatal stressors. To examine whether prenatal medical illnesses differed between groups, we fit a multiple regression model with time (4-week blocks) and group as predictors. Groups were also compared for prematurity, maternal age, and age of survey subjects using *t*-tests.

RESULTS

One hundred and eighty-eight autism surveys (43%), 92 Down syndrome surveys (48%), and 212 control surveys (41%) were returned.

There was no significant difference in prematurity between the autism and control surveys ($t(398) = 0.26$, p = NS). However, the Down syndrome group was significantly more premature for both Down vs. autism ($t(278) = 3.85$, $p = 0.002$) and Down vs. control ($t(302) = 4.54$, $p < 0.00001$) survey comparisons (Table I).

Autism survey participants were significantly younger than Down syndrome survey participants ($t(275) = 2.06$, $p = 0.040$), and Down syndrome survey participants tended to be younger than control survey participants ($t(299) = 1.96$, $p = 0.051$) (Table I).

Maternal age was significantly lower for control surveys than autism ($t(398) = 4.9$, $p < 0.00001$) or Down syndrome ($t(302) = 4.4$, $p = 0.000016$) surveys. However, maternal age did not significantly differ between autism and Down syndrome surveys ($t(278) = 0.78$, p = NS) (Table I).

The incidence of presence of stressors was 32.4 per 100 autism surveys, as compared to 18.9 for control surveys and 21.7 for Down syndrome surveys. χ^2 analysis revealed this incidence to be significantly greater for autism as compared to control surveys ($p = 0.0007$) and a trend for autism greater than Down syndrome surveys ($p = 0.059$). Stressors encountered are summarized in Table II according to the categorization of Holmes and Rahe (1967). For the total number of stressors encountered (allowing for more than one stressor per survey), 44.7 stressors were reported per 100 autism surveys, as compared to 25.9 for control surveys, and 26.1 for Down syndrome surveys. Analysis revealed that the distribution of stressor incidence across the 4-week prenatal blocks did not significantly differ from what would be predicted by the first postnatal block for control surveys or Down syndrome surveys, but did significantly differ for autism surveys ($p < 001$) (Fig. 1). Comparison of the 29–32 week and preceding blocks (21–32 weeks) vs. the other blocks revealed a significant difference for autism ($p < 046$; χ^2) but not Down syndrome or control surveys. Furthermore, the 25–28 week block was significantly outside the 95% confidence band for the quadratic fit of perinatal stressors across prenatal blocks in autism. No other block was outside this confidence interval for autism, Down syndrome, or control surveys. Further analysis of residuals revealed that the prediction error for the 25–28 week block of the autism group was unusually high ($p = 0.0035$, two-tailed).

In order to determine whether child's age (due to impact on recall accuracy) or maternal age (due to differential impact of stressors depending on maternal age) affected incidence of stressors in autism, we compared maternal and child age for surveys with and without stressors at 21–32 weeks. There was no significant difference in the child's age between groups ($t(184) = 1.33$, p = NS) and a trend towards

Table I. Characteristics of Study Population

	Autism (mean ± SD)	Down syndrome (mean ± SD)	Controls (mean ± SD)
Age of child (years)	7.9 ± 4.0	9.0 ± 4.4	10.2 ± 4.9
Male gender (%)	83.5	62.0	49.0
Maternal age (years)	31.2 ± 4.8	31.7 ± 5.3	28.5 ± 6.1
Prematurity (weeks)	1.8 ± 14.3	8.6 ± 12.7	1.5 ± 12.5

Table II. Stressors Encountered

Stressor encountered	Severity score (Holmes & Rahe, 1967)
Divorce	73
Marital separation	65
Death of close family member	63
Injury or medical condition not affecting fetus[a]	53
Marriage	50
Fired at work	47
Change in health of family member	44
Another preganacy	40
Gain of new family member	39
Business readjustment	39
Change in financial state	38
Death of close friend	37
Change to a different line of work	36
Change in number of arguments with spouse	35
New large mortgage	31
Foreclosure on mortgage or loan	30
Change in responsibilities in work	29
Son or daughter leaving home	29
Begin or end school	26
Change in living condition	25
Revision of personal habits	24
Trouble with boss	23
Change in work hours or conditions	20
Change in residence	20
Change in sleeping habits	16

[a]One motor vehicle accident and one pituitary adenoma with no known fetal consequences, which were both recorded in the 'stressors' portion of the survey.

older mothers in the stress group ($t(186) = 3.55$, $p = 0.061$).

The 25–28 week block for autism was also the only outlier among all the groups when adjusted for stressor severity (Fig. 2).

A total of 79 separate medical illnesses were reported. In order to compare maternal prenatal medical illnesses between group and across time, we fit a multiple regression model using log (illness/100) as the response and time (4-week blocks) and group as predictors. We used a quadratic term corresponding to time. There was no interaction effect due to time and group. There was a significant difference between the three groups. We used Tukey's Honest Significant Difference (HSD) *t*-test that compares three groups simultaneously at the 5% level and found that Down syndrome and autism surveys were similar to each other and had a significantly higher rate of maternal prenatal illnesses reported as compared to control surveys (Fig. 3).

There were an insufficient number of surveys indicating a particular medication or group of medications to analyze medications as a prenatal risk factor. Immunizations were rare for all groups.

A greater proportion of autism surveys reported normal language compared to Down syndrome surveys, but a greater number of autism surveys also reported no language compared to Down syndrome surveys.

Post-hoc analysis explored whether autistic children with stressors differed in language development from those without stressors. The group experiencing stressors at 21–32 weeks was compared with those without stressors during this time period. Children currently lacking language were more likely to be in stressor group and those currently having language (normal or impaired) were more likely to be in the without stressor group ($p < 0.036$; Fisher's Exact, two-tailed). Those reporting normal language development did not significantly differ in stressor experience compared to those reporting delayed or no

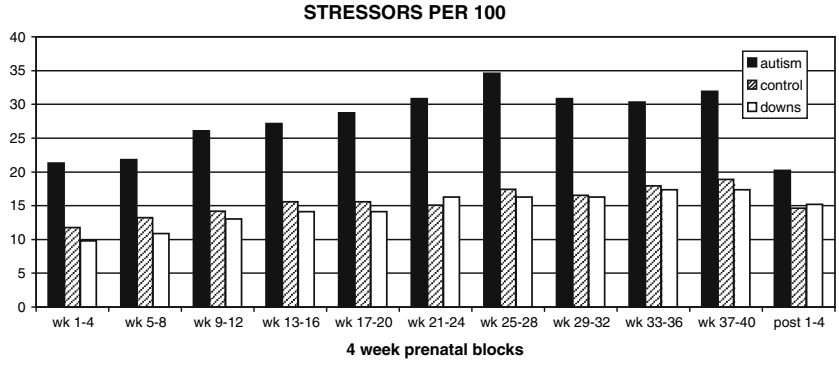

Fig. 1. Number of stressors per 100 surveys for each 4-week block of pregnancy.

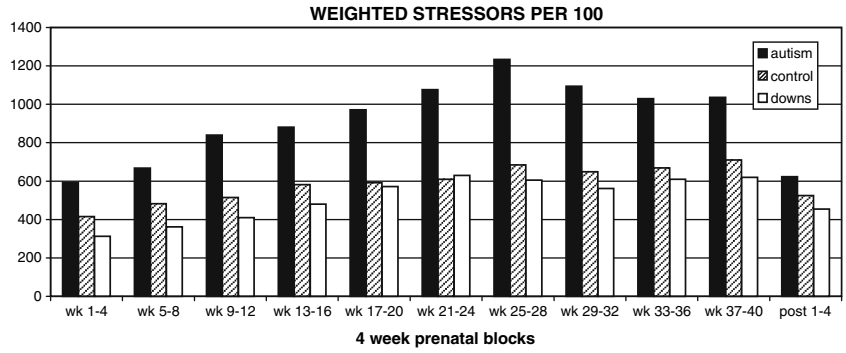

Fig. 2. Weighted stressors per 100 surveys for each 4-week block of pregnancy.

language development ($p = 0.73$; Fisher's Exact, two-tailed).

DISCUSSION

As expected, more prenatal stressors were reported among mothers of autistic children. Whereas this could be of significance, it could be attributed to a response bias since mothers of children with autism may be more likely to recall stressful events during that child's pregnancy. A significant increase in stressors was seen at 21–32 weeks gestation in autism, but not with the Down syndrome or control surveys. This is consistent with the embryological age suggested by neuroanatomical findings seen in the cerebellum in autism (Bailey *et al.*, 1998; Bauman & Kemper, 1994). This pattern would seem less likely attributable to response bias. This same pattern was also found when the stressors were weighted for severity by scores on the SRRS.

Whereas Down syndrome and autism surveys reported more maternal medical illnesses in the prenatal period than control surveys, there was no difference in the temporal pattern across prenatal blocks between groups.

Prematurity did not appear to be a contributing factor to these results, since autism surveys revealed no more prematurity than control surveys. Children with autism surveyed were significantly younger than both children with Down syndrome and children without neurodevelopmental diagnoses. It is possible that the age difference between the groups might have resulted in a response bias, since parents of younger children would have less time to forget details of the prenatal period. However, it would be unlikely to cause the specific pattern with a peak at 25–28 weeks demonstrated. Furthermore, there was no difference in the child's age between the 21–32 week stressor group and the group without stressors during this timeframe among the autism surveys. Another possible confound is that the control groups were limited to a Dartmouth-Hitchcock Medical Center area sample. Due to the general risk of inaccurate recall by parents with retrospective surveys such as this, these findings would ultimately need to be confirmed in a prospective manner. Also, as suggested by the language findings on the surveys, there also appears

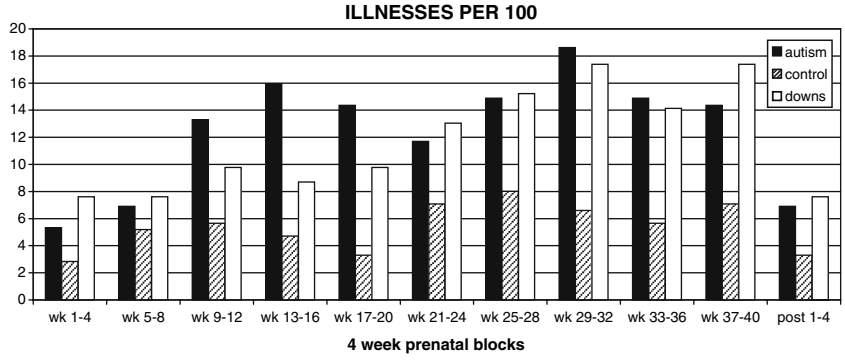

Fig. 3. Number of illnesses per 100 surveys for each 4-week block of pregnancy.

to be some variation in distribution of severity of impairment between the autism and Down syndrome groups that might interact with the findings.

The finding that individuals with autism who experienced prenatal stress at 21–32 weeks were more likely to lack language than other autistic individuals may suggest that autism resulting from prenatal stressors tends to be more severe. However, this finding deserves further investigation before any firmer conclusion could be reached regarding the relationship between prenatal stressors and subsequent language development.

The findings in this study lend some support for the hypothesis that prenatal stress related changes in the brain are a potential etiologic factor in autism. This should be confirmed by larger prospective studies with efforts to match socioeconomic factors, ethnicity, family history, and monitoring subclassifications within autism spectrum disorders. These factors may have differed between groups in our study. Future research is needed in animal models of perinatal stress to better understand the mechanisms that might relate to the specific findings in autism. Research thus far has shown that prenatal stress in rats increases maternal and fetal plasma corticosterone during critical periods of brain development, which can lead to structural changes in the amygdala (Ward *et al*., 2000). These changes in the amygdala result in symptoms often seen in people with autism such as a heightened response to stress, increased fear and diminished social interactions (Takahashi, Baker, & Kalin, 1990; Takahashi, Haglin, & Kalin, 1992; Takahashi & Kalin, 1991; Takahashi, Kalin, Barksdale, Vanden Burgt, & Brownfield, 1988). Research is needed examining the effects of prenatal stress on other areas such as the cerebellum. Cerebellar changes in autism include a decrease in the number of Purkinje cells and granule cells without gliosis in the cerebellar hemispheres (Bauman & Kemper, 1994). The impact of prenatal stress on cerebellar pathology directed at the time periods appropriate for autism has not been studied. However, as stated in the Introduction, the risk of damage to cerebellar granule cells is increased in rats after prenatal exposure to glucocorticoids (Ahlbom *et al*., 2000), which are part of the stress response. Whereas the relationship between the pathology of autism and the pathology of prenatal stress is of interest for future investigation, the current data is far too preliminary to suggest a causative relationship. Future research should focus on the specific developmental periods analogous to our findings in animals in order to determine whether the stress induced behavioral and anatomical changes resemble those in autism. Subsequent prospective studies will be needed to further understand how these mechanisms might affect development in humans and how these might relate to autism.

The question also remains as to whether prenatal stress can serve independently as a risk factor for autism, or whether it might contribute to the development of autism only in genetically at-risk individuals. For example, family members of individuals with autism spectrum disorders have an elevated rate of anxiety disorders (Piven & Palmer, 1999), which may serve as a maternal risk factor due to an increased physiological stress response to stressful events. Future studies could also explore the incidence of autism among births 12–15 weeks after a particularly catastrophic event in the affected metropolitan area.

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