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The influence of systemic lupus erythematosus on fetal development: Cognitive, behavioral, and health trends

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Abstract

In 1985, Gualtieri and Hicks proposed the immunoreactive theory to explain the higher prevalence of childhood neurodevelopmental disorders in males. The theory claimed that male fetuses are more antigenic to mothers, resulting in increased immunologic attack on the developing central nervous system, and increased probability of atypical brain development. Individuals with systemic lupus erythematosus (SLE) provide a unique situation in which to investigate this theory. We evaluated the parent-reported prevalence of five developmental problems (stuttering, other speech problems, hyperactivity, attention deficit, and reading problems) in two groups: 154 individuals ages 8–20 years born to women with SLE, drawn from six cities, and 154 controls of comparable age and sex whose mothers did not have SLE. Controls were drawn from a comparison group ascertained from randomly selected schools in one of the cities. Questions about handedness, immune disorders, and pregnancy and birth complications were also evaluated. Children of SLE mothers were shown to have more evidence of developmental difficulties, immune related disorders, and nonrighthandedness. For developmental problems, these findings were most marked in male children of SLE mothers. These results suggest that maternal immunoreactivity, as represented by women with SLE, may present a special risk factor for subsequent learning difficulties in their children, particularly males. (*JINS*, 1997, *3*, 370–376.)

Keywords: Immunoreactivity, SLE, Learning difficulties, Attention deficit

INTRODUCTION

Several researchers have proposed the idea that maternal immunoreactivity may exert a negative influence on fetal neurodevelopment (Behan & Geschwind, 1985; Denenburg et al., 1991; Adinolfi, 1993). The immunoreactive theory proposed by Gualtieri and Hicks (1985) attempted to explain the higher prevalence of childhood neurodevelopmental disorders in males. The theory suggests that male fetuses may be more antigenic to mothers, resulting in an increased likelihood of maternal immunologic attack on the developing brain, and an increased probability of developmental difficulties in male children. Although the mechanism of the proposed immunologic attack is not known, it is possible that maternal antibodies, particularly immunoglobulin G (IgG) antibodies, which can enter the fetal circulation, could mediate this process (Adinolfi, 1993). Gualtieri and Hicks further suggested that immunoreactive mothers could be identified by the presence of allergies or autoimmune disorders such as SLE. Nonrighthandedness has often been reported to be associated with developmental learning difficulties and immunologic dysfunction (Behan & Geschwind, 1985).

Systemic lupus is a multisystem disease that affects women more frequently than men, in a ratio of 9:1. The disease is characterized serologically by the presence of autoantibodies that are directed against cellular components (antigens). The resulting interaction between these autoanti-

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bodies and their target antigens can lead to the development of inflammatory reactions in various organ systems.

SLE is known to be associated with an increased risk of negative pregnancy outcomes including increased spontaneous abortion rates, intrauterine growth retardation, an increased rate of premature births, and congenital heart block (Rubbert et al., 1992; Petri & Allbritton, 1993). Certain autoantibodies, antiphospholipid antibodies, have been reported to be reliable clinical markers for recurrent fetal loss (Ramsey-Goldman, 1988; Ginsberg et al., 1992; Hayslett, 1992; Ramsey-Goldman et al., 1992, 1993; Kutteh et al., 1993), although the exact pathophysiologic mechanism is not known (Feinstein, 1992; McIntyre, 1992). In addition to fetal loss, an association has been shown between antiphospholipid antibodies and intrauterine growth retardation, preterm delivery, and low birth weight (Adams et al., 1992; Out et al., 1992; Rubbert et al., 1992).

In a large questionnaire-based study involving 468 children and their families, Crawford et al. (1992) reported that children of mothers with various immunologic disorders were more likely to have learning and behavior problems than were those of mothers without allergic or immunologic disorders. This result was also found for children of fathers with immunologic disorders. These findings seem to support a genetic role for the association between immunoreactivity and developmental problems rather than a strictly gestational role. In contrast, Lahita (1988) investigated the prevalence of learning disabilities in the children of parents with SLE and found strong evidence for a gestational role. None of the 13 children of fathers with SLE had learning disabilities, but 45% of the 55 male children of mothers with SLE had a learning disability. Over 90% of the learning disabilities were said to be dyslexia, although Lahita's definition of dyslexia in the offspring of patients with SLE (discrepancy between verbal and performance IQ) is not the present standard in neuropsychology. Of the 35 female children of mothers with SLE, 8% had a developmental problem such as stuttering or dyscalculia; none were dyslexic. One weakness of this study is that the investigator did not control for possible contributions of prematurity or pre- and perinatal complications to the reported differential gender prevalence of developmental problems. A similar study by Ross et al. (1993) reported that 48% of 25 children of mothers with SLE met the criteria for learning disabilities, primarily reading disability; 4 of the children were female, and 8 were male. The rate for learning disabilities in a matched sample was 20%; however, this study did not consider potential genetic influences (i.e., learning disabilities in the rest of the family).

Behan et al. (1985) have also reported evidence that seems to support a gestational role. They analyzed the sera of 132 women whose children ($n = 183$) were dyslexic, in this case clearly defined as a 2-year discrepancy between reading achievement and chronological age. Even though these women did not have autoimmune disorders, their antithyroid antibody levels were 2.5 times higher than expected. In addition, these investigators reported a strong association between dyslexia and congenital heart lesions in the children of these mothers. In a second set of 45 mothers of dyslexic children, anti-Ro sera levels were found to be over 20 times that of controls. Anti-Ro is a maternal autoantibody that may result in congenital cerebral and/or cardiac pathology.

The aim of the present investigation was to examine the association between maternal immunoreactivity and atypical brain development in the child. Our hypothesis was that children of mothers with SLE would show more evidence of atypical brain development (learning difficulties and nonrighthandedness) than would children of unaffected mothers, even after controlling for differential rates of pregnancy and birth complications, and for the prevalence of developmental problems in the rest of the family. We also evaluated immune problems (other than SLE) in the children, because of research that has reported associations between immune disorders, developmental problems, and nonrighthandedness (see Kaplan & Crawford, 1994 for a review; Behan & Geschwind, 1985).

METHOD

Research Participants

A total of 308 children participated; 154 were children of mothers with SLE and 154 were normal control group children attending regular classrooms in the local public schools. The 154 children of mothers with SLE were recruited from an ongoing multicenter SLE assessment project, encompassing six North American cities (Baltimore, MD; Calgary, Alberta, Canada; Nashville, TN; Palo Alto, CA; Pittsburgh, PA; and Saskatoon, Saskatchewan, Canada). The diagnosis of SLE for the mothers of participating children was made by the mother's rheumatologist at the various study sites according to the 1982 American Rheumatology Association criteria for SLE (Tan et al., 1982). The response rate for 345 questionnaires sent out to SLE participants was 61% ($n = 211$), which was considered quite good for a lengthy questionnaire sent to people with a chronic disease involving fatigue. Of the 211 respondents, 57 were excluded because of typical reasons such as the presence of a neurological disorder, having been adopted (since we required birth information), being out of the specified age range, or because the mothers reported having a comorbid disorder such as rheumatoid arthritis. For practical reasons, the normal controls were selected from an existing database in Calgary (Crawford et al., 1992) that used the same questionnaire measures. For this database, more than 1,000 children attending regular classrooms in the public school system had been given questionnaires to take home to their parents. The normal controls had attended Grades 4 through 12 in randomly selected public schools throughout the entire city. Controls were a group of children of comparable age and sex, whose mothers did not have SLE. In each group, there were 85 male and 69 female children. The average age in each group was 13.76 years, with a standard deviation of 3.12 for con-

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trols and 3.22 for children of SLE women. Socioeconomic status (SES) as measured by the Blishen SES index (Blishen et al., 1987) did not differ between the two groups [univariate $F(1,207) = 0.81$].

Measures

A questionnaire was completed by the mothers of the 308 children. It included measures, for both the child and his/her family members, of handedness (Crovitz & Zener, 1962), five developmental problems including stuttering, other speech problems such as difficulty with pronunciation, hyperactivity, attention deficit, and reading difficulties (Burke et al., 1988), and immune disorders (all of which were based on parent report) including allergies, hay fever, asthma, bowel disease, allergic skin reactions, thyroid disease, and insulin dependent diabetes mellitus (Burke et al., 1988). Pregnancy and birth complications were also determined (Levine, 1980). Pregnancy risk factors included bleeding in the first, second, and/or third trimesters, toxemia, smoking during pregnancy, induced labor, delivery by Caesarean section, difficult delivery, put to sleep for delivery, medications during pregnancy, infections during pregnancy, and other pregnancy problems. Birth complications included injury during birth, breathing problems, jaundice, cyanosis, being a twin or triplet, seizures, need for supplemental oxygen, problems sucking, more than 7 days in the hospital, born with a heart defect, and born with another birth defect. Modifications of the scoring protocols outlined by Burke et al. (1988) and Levine (1980) were used for items relating to developmental and immune problems, and pregnancy and birth complications, respectively. The indices used in analyses for developmental problems, immune disorders, and pregnancy and birth complications were calculated with a weighting system based on the closeness of the relative (e.g., presence of a problem in a first degree relative was weighted more heavily than in a second degree relative). The pregnancy and birth complications index was calculated with a straight addition of the risk factors checked by the mother on the questionnaire.

For both the χ^2 and analysis of variance results, alpha was partitioned according to the Bonferonni correction procedures.

RESULTS

Prevalence of Developmental Problems, Immune Problems, and Nonrighthandedness in the Child

Group differences for the five developmental problems in the child were analyzed using the χ^2 statistic (Table 1). At the .05/5 = .01 level of significance, male SLE group children were found to have significantly more hyperactivity, attention, and reading problems as compared to male normal control group children. In contrast, female SLE children did not differ from controls, except for one finding of marginal significance ($p < .05$) in which there was a higher prevalence of hyperactivity in the SLE group. Prevalence rates for these disorders are in Table 2.

Table 1. Chi-square analyses of child developmental problems

Variable	χ^2	*df*
Developmental problems (males and females)		
Stuttering	2.22	1
Pronunciation problems	4.18	2
Hyperactivity	16.28**	2
Attention problems	7.32**	1
Reading difficulties	8.65**	1
Developmental problems (males only)		
Stuttering	1.02	1
Pronunciation problems	3.35	2
Hyperactivity	9.80**	1
Attention problems	6.39**	1
Reading difficulties	7.91**	1
Developmental problems (females only)		
Stuttering	1.94	1
Pronunciation problems	0.94	1
Hyperactivity	6.01*	1
Attention problems	1.26	1
Reading difficulties	1.32	1

*$p < .05$, **$p < .01$.

Immune disorders in the child were analyzed using the χ^2 statistic. At an adjusted alpha level of .05/6 = .008, children in the SLE group had significantly more reports of allergies ($\chi^2[1] = 9.32$, $p = .002$), hay fever ($\chi^2[1] = 12.25$, $p = .0005$), skin reactions ($\chi^2[1] = 11.99$, $p = .0005$), and bowel disease ($\chi^2[1] = 9.15$, $p = .002$) than children in the normal control group. A marginal group difference ($\chi^2[1] = 5.92$, $p = .015$) was found for thyroid disease with a higher prevalence in SLE group children. Separate chi-square analyses for the same variables were conducted to examine gender differences between groups. At the .05/6 = .008 level of significance, male SLE group children were found to have a significantly higher prevalence of skin reactions as compared to normal males ($\chi^2[1] = 7.65$, $p = .006$). Male SLE group children also had marginally higher levels ($p < .05$) of allergies, hay fever, bowel disease, and thyroid disease as compared to male normal control group children. In contrast, female SLE group children had a significantly higher level ($\chi^2[1] = 7.26$, $p = .007$) for hay fever as compared to normal group females. Female SLE group children also had marginally higher levels ($p < .05$) of allergies, skin reactions, and bowel disease as compared to normal control group females.

Child handedness was examined using univariate analysis of variance. A significant main effect for group was found with children of SLE mothers demonstrating more nonrighthandedness than normal control group children [$F(1,302) = 4.92$, $p = .027$]. The Gender × Group interaction was not significant, nor was the main effect of gender.

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Table 2. Prevalence rates of developmental problems

	Males and females		Males		Females	
Developmental problem	Frequency	%	Frequency	%	Frequency	%
Normals						
Stuttering	3/149	2.01	3/83	3.62	0/66	0
Pronunciation	7/149	4.70	6/83	7.23	1/66	1.51
Hyperactivity	2/149	1.34	2/83	2.41	0/66	0
Attention	9/150	6.00	7/83	8.43	2/67	2.99
Reading	14/150	9.33	10/83	12.05	4/67	5.97
SLE						
Stuttering	8/153	5.23	6/84	7.14	2/69	2.90
Pronunciation	14/153	9.15	11/84	13.10	3/69	4.35
Hyperactivity	20/153	13.07	14/84	16.67	6/69	8.70
Attention	24/153	15.69	19/84	22.62	5/69	7.25
Reading	33/153	21.57	25/84	29.76	8/69	11.59

Prevalence of Developmental Problems, Immune Problems and Nonrighthandedness in the Family

The overall familial prevalence, excluding the child, of developmental problems was analyzed using an ANOVA. The Gender × Group interaction was not significant, nor were the main effects for group or for gender.

Univariate results from the ANOVA conducted on the total familial immune disorder index, excluding the child, were as follows. A significant main effect for group was found with more immune disorders in SLE group families [$F(3,212) = 16.52$, $p < .001$]. A subsequent MANOVA was used to examine familial prevalence, excluding the child, of the various types of immune disorders. At the $.05/2 = .025$ level of significance, a significant main effect of group was found, so the univariate F tests for the separate dependent variables were examined. Significantly higher levels [$F(1,214) = 23.78$, $p < .001$] of bowel disease were found in SLE families. Marginally higher levels ($p < .05$) of skin reactions and thyroid disease were also found in SLE families; however, these findings did not retain significance at the adjusted alpha level.

The overall familial handedness index, calculated with the child excluded, was also examined using an ANOVA. A significant main effect for group was found, with SLE group families reporting more nonrighthandedness as compared to normal controls [$F(1,213) = 9.15$, $p = .003$]. No other findings were significant.

Controlling for the Possible Influence of Pregnancy and Birth Complications

A higher prevalence of pregnancy complications and lower birth weights are well documented factors in children born to women with SLE. Our analyses confirmed this pattern: the SLE group had higher scores on the pregnancy complications index [$F(1,245) = 9.25$, $p = .003$]. There was no difference between male and female children of women with SLE. Separate χ^2 tests of the individual variables revealed that the SLE group reported a higher prevalence of Caesarean sections [$\chi^2(1) = 8.35$, $p = .004$], medications taken during pregnancy [$\chi^2(1) = 8.70$, $p = .003$], and other pregnancy problems [$\chi^2(1) = 8.25$, $p = .004$]. One group difference of marginal significance ($p < .05$) was found for being put to sleep for delivery with more occurrences in the SLE group. The SLE mothers also had significantly lower birth weight babies [$F(1,289) = 11.63$, $p = .001$].

As a result of these findings, a MANCOVA was conducted to determine whether group differences for child indices would retain significance after controlling for the higher prevalence of pregnancy complications and lower birth weights in the SLE group. Child birth weight was shown to have a marginally significant negative correlation with the pregnancy complications index [$r(291) = -.149$, $p < .05$]. Although the magnitude of this correlation is modest, it suggested that only one of the variables should be entered as a covariate; we selected the pregnancy complications index. Dependent variables used were the indices for child handedness, developmental problems, and immune problems. Multivariate and univariate results are given in Table 3. After controlling for the higher prevalence of pregnancy complications in the SLE group, significant main effects for group and for gender were found, so the univariate F tests were examined. At an adjusted alpha level of $.05/3 = .017$, significant group differences were found with higher levels of both developmental and immune problems in SLE group children. Handedness was found to be marginally significant ($p < .05$), with higher levels of nonrighthandedness in the SLE group. Again, using a corrected alpha level of $.05/3 = .017$, a significant gender difference was found at the univariate level, with more developmental problems (stuttering, other speech problems, reading, attention, and hyperactivity) evident in male children of both groups.

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Table 3. Multivariate and univariate results for child handedness, developmental problems, and immune problems using prevalence of pregnancy complications as a covariate

Source	Multivariate $F(3,280)$	Dependent variables	Univariate $F(1,282)$
Gender × Group	1.13	Handedness	0.24
		Developmental problems	3.01
		Immune problems	0.00
Group	16.00**	Handedness	4.58*
		Developmental problems	19.60**
		Immune problems	31.71**
Gender	5.32**	Handedness	0.59
		Developmental problems	15.08**
		Immune problems	0.19

*$p < .05$, **$p < .01$.

A final attempt to explore the possibility that child developmental outcomes were associated with the variables discussed above consisted of conducting a series of logistic regressions in which the predictor variables were based in part on the significant group differences found in the preceding analyses. For these analyses, only males were used ($n = 168$), because of the above-mentioned finding of a higher developmental problems index in males, when the higher prevalence of pregnancy complications in the SLE group was statistically controlled. The predictor variables were the child's birth weight, Caesarian section performed, being put to sleep for the delivery, medications during pregnancy, other pregnancy problems, and the mother's status (i.e., SLE versus control). The five pregnancy-related variables were entered into the logistic regression first, in order to control for their effects. The mother's status was subsequently entered into the equation. The dependent variable for the first logistic regression was the presence or absence of hyperactivity in the child, the presence or absence of reading problems in the child was the dependent variable for the second logistic regression, and the presence or absence of attention problems was the dependent variable for the final logistic regression.

Of all the variables examined, only the mother's status was a significant predictor of the presence or absence of hyperactivity in the child. The odds ratio (OR) for the association between hyperactivity and maternal SLE was 7.24 (95% C.I.: 1.53, 34.37).

The mother's status was also the only significant predictor of reading problems in the child, after controlling for the five pregnancy-related variables. The OR for the association between reading problems and maternal SLE was 4.06 (95% C.I.: 1.67, 9.87).

The mother's status and other pregnancy problems were significant predictors of the presence or absence of attention problems in the child, once the pregnancy-related variables were controlled for. Holding other pregnancy problems constant, the OR for the association between attention problems and maternal SLE was 3.08 (95% C.I.: 1.08, 8.79).

DISCUSSION

This study has found some evidence in support of an association between maternal immunoreactivity, as represented by women with SLE, and adverse child developmental outcome, particularly in male children. Analyses consistently showed that children of SLE mothers, especially males, had significantly more hyperactivity, attention deficit, and reading difficulties. In contrast, female children of SLE mothers did not differ significantly from female children in the control group with respect to developmental problems. It is important to note that the overall prevalence of developmental problems in the relatives of the children examined in the study did not differ between SLE and control groups, suggesting a gestational rather than a genetic process mediating the higher prevalence of developmental problems in male children of SLE women. Results from the logistic regression analyses provide additional evidence for an association between SLE and risk to the child for the development of hyperactivity, reading problems, and attention deficit. These findings are consistent with those of Crawford et al. (1992), Lahita (1988), and Ross et al. (1993).

While significantly higher rates of immune disorders and nonrighthandedness were found for children of SLE mothers, the familial prevalence of immune disorders and nonrighthandedness was also higher in the SLE group as compared to control families. This would suggest a genetically mediated process for the higher rates of immune disorders and nonrighthandedness in SLE children rather than a strictly gestational process.

Results from this investigation suggest that there is something unique in the SLE group as a whole, independent of disease activity at the time of pregnancy, disease severity during pregnancy, medications taken during pregnancy, pregnancy and birth complications, or child birth weight that confers a heightened risk to the child for subsequent developmental problems. On the other hand, this study suffered from several shortcomings that must be considered in the interpretation of the results. It is possible that the develop-

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mental problems studied would be influenced by the home environment created by the presence of maternal disease. This study was unable to access an appropriate chronic disease control group to evaluate this possibility. In addition, although the current study drew on samples from across North America, the final sample size was still modest. In addition, as in any questionnaire study, the data are dependent upon the memory and recall of the mother providing the information. It is a reasonable assumption that recall bias would influence some of the variables included in this study (e.g., pregnancy and birth complications are probably recalled more strongly by women with SLE). On the other hand, it is less likely that recall bias would threaten the validity of the data provided on the developmental variables (e.g., reading problems, attention problems).

Another methodologic weakness in our study was that parents were only asked to report the presence or absence of each developmental problem. Consequently, our categorization of the children with respect to developmental problems was not based on the formal criteria typically used for a psychiatric diagnosis. Although this limitation makes the conclusions of the study more tenuous, the measures that are typically used to evaluate developmental difficulties are themselves dependent on parental report of presence or absence of symptoms, similar to the method used here. In support of the validity of our method, we note that the prevalence rate (see Table 2) obtained in our normal comparison group for attention problems (6.0% overall, 8.4% for boys and 2.9% for girls) is remarkably similar to the best epidemiologic data available from community samples, the Ontario Child Health Study (OCHS: 10.1% for boys and 3.3% for girls; Offord et al., 1987). The OCHS data were based on the disorder "hyperactivity," but our parents seemed to conservatively estimate the symptom of hyperactivity (see Table 2) while more closely matching the OCHS results in the category of "attention problems."

One other important argument in support of the validity of our results is the fact that parent-reported developmental problems were higher for only the male children of women with SLE: If our findings were significantly attributable to the stresses of having a chronic disease, then the group difference should have been stronger in the female children also.

While the findings of the current study seem to support the original immunoreactivity theory proposed by Gualtieri and Hicks in 1985, the mechanism linking maternal immunoreactivity to child developmental problems was not addressed in the current study. Gualtieri and Hicks specifically proposed a fetal antigenicity mechanism. They hypothesized that, on average, male fetuses are more antigenic than females, and therefore maternal immunologic attack on the male fetus would be more likely. For this reason, higher rates of pregnancy and birth complications would be expected in male as compared to female children. In the current study, comparisons of male and female children of SLE mothers did not reveal significant sex differences for overall rates of pregnancy or birth complications. Moreover, the literature seems to suggest that the potential risk factor for developmental problems in children of SLE mothers is associated with maternal autoantibodies rather than fetal antigenicity (Behan et al., 1985; Lahita, 1988; Ross et al., 1993). In this regard, one possible speculative explanation for the increased risk of developmental problems in this group of children is that circulating maternal autoantibodies such as anti-Ro and/or antiphospholipid antibodies may be present and may target certain brain tissues during gestation and/or for a few months postnatally (Wolin & Steitz, 1984; Behan et al., 1985; Behan & Geschwind, 1985; Adinolfi, 1993).

In summary, these results provide some confirmation that maternal immunoreactivity creates a special risk factor for the children of women with SLE, especially the male children. The fact that there was no group difference in familial prevalence of the five developmental problems tends to rule out a genetic etiology as an explanation for our findings. Future research will need to identify an appropriate chronic disease to control for the environmental influences caused by maternal disease, and to attempt to replicate the current results with direct cognitive assessments of similar groups of children.

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