Effects of Mothers’ Autoimmune Disease During Pregnancy on Learning Disabilities and Hand Preference in Their Children

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Objectives: To determine whether children (and particularly sons) of women with systemic lupus erythematosus (SLE) during pregnancy are more likely to have learning disabilities (LD) and be non–right-handed, and if maternal disease variables (ie, presence of maternal antibodies, disease activity level, and use of corticosteroids) predict the prevalence of LD in offspring.

Design: Case-controlled study with subjects matched by age and sex.

Participants: We studied 58 children whose mothers had SLE during pregnancy and 58 children of healthy mothers.

Measures: Data collected included maternal disease variables in women with SLE during their pregnancies. All children took a standardized intelligence test (Wechsler Intelligence Scale for Children–III) and completed a modified version of the Edinburgh Hand Preference Questionnaire. They also took standardized tests of reading, arithmetic, and writing achievement. Learning disability was defined as having an academic achievement score of at least 1.5 SDs below the Full-Scale IQ.

Results: Sons of women with SLE were significantly more likely to have LD than daughters of women with SLE or children of either sex in the control group. Maternal SLE was not associated with non–right-handedness in sons or daughters. The presence of anti-Ro/La antibodies and disease activity (flare) in mothers during pregnancy were significantly related to higher prevalence of LD in offspring.

Conclusions: Autoimmune disease in women during pregnancy is associated with an increased risk for LD in their sons. Maternal antibodies, particularly anti-Ro/La, likely affect the fetal brain of male offspring and result in later learning problems. These findings should promote greater awareness of the risk for LD in sons of women with autoimmune disease and the possible need for early educational intervention in those children.

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Systemic lupus erythematosus (SLE) is a serious autoimmune disease that affects approximately half a million people in the United States, about 90% of whom are women.1 In SLE, the immune system, instead of serving a protective function, attacks healthy connective tissues and organs and causes painful, disabling, and sometimes life-threatening tissue inflammation and injury. Systemic lupus erythematosus often is associated with the presence of autoantibodies, including those directed against double-stranded DNA and extractable nuclear antigens, termed Ro (SS-A), La (SS-B), Sm, and RNP (U1 RNP or nuclear RNP). Some literature has suggested that children of women with SLE are significantly more likely to have developmental disorders, since maternal autoantibodies can cross the placenta and theoretically impair fetal brain development.2-4

Preliminary research has found that offspring of women with SLE, particularly boys, are more likely to have developmental disorders such as learning disabilities (LD), stuttering, and attention-deficit/hyperactivity disorder. In one study,3 a significant number of patients with SLE reported that their sons had LD, including dyslexia in more than 90%. Left-handedness was not associated with LD. In another study,6 women with SLE reported that their sons had developmental difficulties such as reading and attention problems and were left-handed or ambidextrous significantly more often than did mothers of children in a same-age and -sex control group.

Evidence already exists that maternal antibodies may affect the fetus. For example, offspring of some women with SLE have a higher frequency of congenital heart block, rash, and other transient symp-
toms of SLE, a symptom complex termed neonatal lupus erythematosus.7-9 Studies have linked the presence of anti-Ro and anti-La antibodies in mothers to risk for neonatal lupus erythematosus in their children.10 Support for a relationship between the presence of maternal antibodies and LD in offspring is found in a study showing that serum levels of the anti-Ro antibody in mothers of dyslexic children were 20 times higher than those of mothers of children without dyslexia.11

The major aims of the current study were to verify the increased prevalence of LD and non–right-handedness in children, particularly sons, of women with SLE and to determine whether the presence of maternal antibodies, lupus disease activity, or use of corticosteroids during pregnancy is associated with LD in the children.

Although previous studies reported a significantly higher prevalence of LD10 and non–right-handedness8 in sons of women with SLE, those studies relied on questionnaires to parents, rather than results of direct examination of the children. Therefore, those results might have been biased. In addition, neither study provided data on the presence and type of maternal autoantibodies, information that is important for assessing an immunoreactivity theory.

METHODS

SAMPLE DESCRIPTION

The study included 58 offspring of women who had SLE before and during their pregnancies and had no other medical diagnoses. Another 58 children (control subjects) were born to women who were in good health and had no documented medical illnesses before and during their pregnancies. The offspring included in the study ranged in age from 8 to 15 years. Eight years of age is considered the earliest appropriate time to assess the presence of dyslexia in children,12 and the same standardized tests may be used for children and adolescents aged 8 to 15 years.

The offspring in the study group were the sons and daughters of 58 women with SLE among 66 who had been studied prospectively during their pregnancies and post partum at the Hospital for Special Surgery, New York, NY, from January 1, 1985, through December 31, 19898,13 and who had live births. The women were receiving medical care at New York Presbyterian Hospital–Cornell Medical Center, New York, at the time of pregnancy and were referred to the study by their physicians, because lupus is a high-risk condition and frequently results in pregnancy loss.13

This follow-up study was initiated just before the first children of these women turned 8 years of age. Attempts were made to locate and recruit the children for the study until the year 2001. Eight of the women from the potential sample did not participate in the follow-up study, because it was not possible to locate 6 of them and 2 refused participation.

Each child in the control group was selected consecutively from the birth registry at New York Presbyterian Hospital to match on age (within 3 months) and sex with a child in the SLE group until a match was achieved. Children with birth weights of less than 2500 g and gestational ages of less than 37 weeks were considered to be premature. Social class categories were determined by means of the Hollingshead Scales.14

The mothers of the children were contacted first by mail and then by telephone by the investigators. The study was approved by the Institutional Review Board at Weill Medical College of Cornell University, New York, and the investigators received written consent from the parents and assent from the children.

Table 1 lists the demographic and neonatal variables for the study and control groups. Most of the children were white and from middle- to upper-middle–class homes. Differences between any of the variables shown were not significant by t test and χ² analyses.

DESCRIPTION OF VARIABLES

Maternal

Data were available for each of the mothers with SLE on physician-estimated level of disease activity during pregnancy and the presence or absence of autoantibodies to Ro, La, Sm, and RNP by immunodiffusion techniques. Screening tests for the autoantibodies were conducted on the first serum specimen obtained during pregnancy and were tested at least once each trimester. Antibody levels did not change notably during pregnancy. The researchers also recorded use of medication, primarily corticosteroids, to treat SLE during the pregnancies. The treating physician (M.L.) estimated disease activity of SLE (flare) by using the New York Hospital for Special Surgery Disease Activity Scale.15 The score for the scale is based on the presence of 11 clinical signs (eg, rash, serositis, and mucosal ulcers) and 8 laboratory variables (eg, creatinine level, platelet count, and erythrocyte sedimentation rate) with a score of present or absent on each. This instrument has been shown to correlate highly with 5 other measures of SLE disease activity (correlation range, 0.81-0.97), with the physician’s clinical impression of disease, and with the patient’s self-reported disease activity scores.16 For this study, however, disease activity for the pregnancy overall was based on the treating physician’s global assessment of activity (flare) or no activity.
Children

A psychologist used standardized tests of intelligence and academic achievement to evaluate each child. Intelligence was measured with the Wechsler Intelligence Scale for Children—III (WJ-R ACH), a standardized intelligence test that provides a Full-Scale IQ (FSIQ) score for children ranging in age from 6 years to 16 years (50 to 50 months). The psychologists who administered the tests to the children were considered to be masked to the group, because they were not informed of the purpose of the study or that there were 2 groups (SLE and control). Rash, arthritis, and hair loss are physical manifestations of lupus, but these symptoms were relatively uncommon in this group of mothers with SLE, and it is not likely that the psychologists would have recognized the symptoms as distinguishing one group of mothers from another.

Academic achievement was assessed through subtests of the Woodcock Johnson Achievement Test—Revised (WJ-R ACH) and the Gray Oral Reading Tests—III (GORT-III). Subtests from the WJ-R ACH that were used include Word Attack, which measures ability to read nonsense words and provides a measure of reading decoding skills; Calculation, which measures math calculation abilities; and Writing Samples, which measures skills in writing responses to a variety of demands. The reading subtests of the WJ-R ACH primarily measure word recognition skills, with reading comprehension, particularly of a more inferential nature, only minimally assessed. Therefore, the WJ-R ACH was used to assess only reading decoding skills, and the GORT-III was administered to assess ability to read words in context and reading comprehension. The GORT-III provides standard scores for oral paragraph reading, based on speed and accuracy (Passage Score); for reading comprehension, based on information read (Comprehension Score); and for both measures combined (Oral Reading Quotient).

The Wechsler FSIQ score and each score from the WJ-R ACH and GORT-III are based on a mean of 100 and an SD of 15. Therefore, it is possible to directly compare IQ and achievement scores.

CLASSIFICATION OF LD

Despite considerable debate regarding the best method of defining LD, children in this study were categorized as having LD according to a discrepancy measure. Specifically, they were considered to have LD if they had an academic achievement score that was at least 1.5 SDs (22 points) below their FSIQ scores. This definition has been used in other research on LD. Children with FSIQ scores of 70 or less were classified as mentally deficient, rather than learning disabled, regardless of the FSIQachievement score discrepancy, because it was expected that learning difficulties in those cases would reflect global intellectual limitations.

Information also was obtained from each child’s school on the following 2 different measures: (1) school status, ie, whether the child was retained in school, received remediation (tutoring and resource room), was in a special class, or attended a special school; and (2) the basis for special education services, according to New York State classification (eg, language impairment, LD, mental retardation, and visual impairment). That information was obtained to determine whether there was a correspondence between the school and the study classifications of the child.

EVALUATION OF HANDEDNESS

Children also completed a version of the Edinburgh Handedness Questionnaire, modified for children. They were asked to show their hand use on 10 tasks, including eating with a fork, holding a pencil, and throwing a ball, and then to rate the hand use as always right, usually right, left or right, usually left, or always left. A score of 1 was assigned to always right, and a score of 5 for always left. Therefore, a child with a score of 10 would be considered extremely right-handed; one with a score of 50, extremely left-handed. Children with scores from 11 through 20 were considered right-handed; those with scores from 21 through 39, ambidextrous; and those with scores from 40 through 50, left-handed. The categories were collapsed into right-handed (≤20) and non–right-handed (>20), because the question of interest was whether the child was right-handed.

ANALYTIC STRATEGY

To assess differences in group and sex on overall IQ and academic achievement scores, we conducted an analysis of variance with FSIQ as the dependent variable, and a multivariate analysis of variance with academic achievement scores as the dependent variables.

Logistic regression analyses were conducted to determine whether FSIQ and any of the demographic and perinatal variables listed in Table 1 were significantly related to LD and hand preference category, respectively, and should be used as covariates. The analyses showed that only birth weight was significantly related to LD, and that none of the predictor variables entered was significantly related to hand preference category.

We then performed 3 multiple logistic regression analyses. In the first analysis, presence of LD was the dependent variable, with group, sex, group × sex, and birth weight as the predictor variables. In the second analysis, hand preference category was the dependent variable, with group, sex, and group × sex as the predictor variables. The third logistic regression analysis was conducted solely for the children whose mothers had SLE, with LD as the dependent variable and the presence of maternal antibodies to the extractable nuclear antigens Ro, La, Sm, or RNP; disease flare; maternal use of corticosteroids; birth weight; and sex as the predictor variables. Presence of antibodies to the extractable nuclear antigens was analyzed as positive for anti-Ro and/or anti-La (ie, positivity to either or both treated as a single variable) and positive for anti-Sm and/or anti-RNP (treated as a single variable). The results of the logistic regression analyses are presented as odds ratios (ORs) and their 95% confidence intervals (CIs). In all analyses, a probability level of .05 was considered significant.

OUTCOME OF CHILDREN

IQ/Academic Achievement

As seen in Table 2, children of women with SLE and controls had mean IQ scores that generally were high average (high-average range for IQ scores, 110-119). There was no significant difference in overall IQ according to group, sex, or group × sex. Three children in the SLE group and 1 child in the control group had FSIQ scores below the low-average range (<80). All were born prematurely. Their FSIQ scores (birth weights) were 75 (992 g), 79 (1145 g), 72 (1695 g), and 78 (981 g).

We found no significant effects of group or sex on academic achievement scores, but there was a significant interaction between group and sex (F1,108 = 2.28; P < .05). Specifically, we found significant group × sex interactions on the GORT-III (F1,116 = 5.13; P < .03) and the
Woodcock Johnson Writing Sample (F_{1,116}=6.96; P<.01), but not on the other academic achievement tests. Boys in the SLE group attained significantly lower scores on the Gray Oral Reading Quotient and lower Writing Sample scores than boys in the control group and girls in both groups (P<.05, by Newman-Keuls tests).

Learning Disability

Of the children in the study categorized as having LD, 8 were in reading only, 7 in reading and writing, 2 in math calculation, 1 in writing, and 1 in math calculation and writing. There was no significant difference between the number of children classified as having LD by the study and by their schools. Five children, in all, were classified differently in the study and by the schools. In 3 cases, in which the investigators classified children as having LD and the school did not, the children were functioning at grade level academically, but they had a significant discrepancy between their academic achievement scores and their FSIQ scores. In the other 2 cases, children classified as having LD by the school but not by the study had FSIQs in the 80s, and there was no significant discrepancy between their academic achievement and their FSIQ scores.

Group × sex interaction significantly predicted prevalence of LD in offspring at the P<.005 level (OR, 0.30; 95% CI, 0.13-0.69). Significantly more sons in the SLE group were classified as having LD than daughters in the SLE group or sons and daughters in the control group (Table 3). Birth weight also significantly predicted LD among children at the P<.006 level (OR, 1.00; 95% CI, 0.998-1.00). No other predictor variables reached enough significance to be included in the model.

Handedness

Table 3 shows the number of boys and girls in the SLE and control groups who were determined to be non–right-handed. None of the independent variables included in the logistic regression analysis significantly predicted hand preference category. Thus, we found no significant difference by group, sex, or group × sex on the number of children who were right-handed vs non–right-handed.

ASSOCIATIONS WITH MATERNAL DATA

Only the presence of anti-Ro/La antibodies and maternal flare during pregnancy significantly predicted LD in the offspring of women with SLE (Table 4), independent of the other variables entered in the model (P<.03). The OR for the association between maternal anti-Ro/La antibodies and LD in the children was 5.74 (95% CI, 1.39-23.74); the OR for the association between ma-

### Table 2. Mean IQ and Academic Achievement Scores for Children in the SLE and Control Groups

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th></th>
<th>Girls</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SLE Group</td>
<td>Control Group</td>
<td>SLE Group</td>
<td>Control Group</td>
<td>SLE Group</td>
<td>Control Group</td>
</tr>
<tr>
<td>FSIQ score</td>
<td>109.1 (17.22)</td>
<td>115.7 (15.3)</td>
<td>113.3 (12.0)</td>
<td>111.3 (13.4)</td>
<td>111.1 (15.0)</td>
<td>113.5 (14.5)</td>
</tr>
<tr>
<td>Academic achievement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gray Oral Reading</td>
<td>98.9 (19.2)</td>
<td>110.4 (17.5)</td>
<td>111.4 (16.9)</td>
<td>109.1 (13.2)</td>
<td>105.0 (19.0)</td>
<td>109.8 (15.4)</td>
</tr>
<tr>
<td>Quotient†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word Attack</td>
<td>110.2 (18.3)</td>
<td>113.5 (16.1)</td>
<td>115.7 (16.9)</td>
<td>115.1 (16.8)</td>
<td>112.9 (17.7)</td>
<td>114.3 (16.3)</td>
</tr>
<tr>
<td>Calculation</td>
<td>114.5 (21.9)</td>
<td>112.4 (17.4)</td>
<td>115.6 (17.5)</td>
<td>122.3 (16.8)</td>
<td>115.0 (19.8)</td>
<td>112.4 (17.0)</td>
</tr>
<tr>
<td>Writing Sample‡</td>
<td>98.2 (17.1)</td>
<td>107.8 (12.1)</td>
<td>109.6 (12.2)</td>
<td>106.4 (8.0)</td>
<td>103.7 (15.8)</td>
<td>107.1 (10.2)</td>
</tr>
</tbody>
</table>

Abbreviations: FSIQ, Full-Scale IQ; SLE, systemic lupus erythematosus.
*Groups are described in the “Sample Description” subsection of the “Methods” section.
†P<.05.
‡P<.01.

### Table 3. Boys and Girls With LD and Non–Right-handedness in the SLE and Control Groups

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th></th>
<th>Girls</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SLE Group</td>
<td>Control Group</td>
<td>SLE Group</td>
<td>Control Group</td>
<td>SLE Group</td>
<td>Control Group</td>
</tr>
<tr>
<td>LD</td>
<td>11</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Reading†</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Math calculation</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Writing</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Non–right-handedness</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: LD, learning disabilities; SLE, systemic lupus erythematosus.
*Groups are described in the “Sample Description” subsection of the “Methods” section.
†Consists of Word Attack, passage reading, and reading comprehension.
ternal flare and LD in the children was 9.43 (95% CI, 1.32-67.24). Thus, autoantibodies for Sm/RNP, use of corticosteroids, birth weight, and sex were not related to the presence of LD in offspring of women with SLE, independent of the presence of anti-Ro/La antibodies and maternal flare. A post hoc analysis also showed that the mothers of sons were significantly more likely to have anti-Ro/La antibodies ($\chi^2 = 7.3; P < .01$).

This study found that sons of women with SLE during pregnancy are significantly more likely to have LD than sons of women who were healthy during pregnancy and than daughters of both groups of women; that hand preference in offspring is not related to maternal SLE; and that disease activity and presence of anti-Ro/La antibodies in mothers with SLE are associated with LD in their children. It should be noted, however, that the CIs for the relationship between maternal SLE and LD in boys and for the associations between the significant maternal illness variables and LD are large.

Nonetheless, the results of this study provide a more valid confirmation of similar findings from 2 previous studies, since those studies relied on parental reports, rather than on direct and standardized testing results of the children. The prevalence of LD among sons of women with SLE in this study was 37% (11/30 sons), compared with 10% (3/30 sons) among the sons of control women. The rate of 37% is somewhat lower than the 44% found through one survey and somewhat higher than the 30% (for reading disorders only) derived from a multicenter questionnaire study.

Although 15 (26%) of the children of mothers with SLE had some form of LD, this result does not represent a dire prognosis. Only 3 of the children in the SLE group had IQ scores that were less than 80 and were in special education classes, and each of those children had been born very prematurely (gestational age, <32 weeks). Moreover, children in the SLE group with LD generally had average or better FSIQ scores, and most were already receiving help through a resource room and other tutoring to improve their academic achievement.

The generally higher-than-average intelligence scores of the children suggests the possibility that our use of a discrepancy definition would increase the number of children who were considered to have LD. It is likely that children, particularly in the lower grades, may not have had sufficient academic experience to have achievement scores that are comparable to their relatively high FSIQ scores. Therefore, it was not surprising that 3 of the children with well-above-average IQ scores, classified as having LD by the study criteria, were not recognized as having LD by their schools. Nonetheless, we found relatively little discrepancy between the number of children classified as having LD by their schools and the study. Furthermore, there was no significant difference between the SLE and control groups on mean FSIQ score, so that the preponderance of children with LD in the SLE group cannot be attributed to higher intelligence scores.

Our finding that sons of women with SLE were not significantly more likely to be left-handed or ambidex-

### Table 4. Learning Disabilities in Offspring as Related to Presence of Maternal Antibodies, Disease Flare, and Use of Corticosteroids During Pregnancy

<table>
<thead>
<tr>
<th>Pregnancy Condition</th>
<th>LD (n = 15)</th>
<th>No LD (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Ro/La antibodies*</td>
<td>7 (47)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Sm/RNP</td>
<td>1 (7)</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Flare†</td>
<td>4 (27)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Use of corticosteroids</td>
<td>6 (40)</td>
<td>14 (33)</td>
</tr>
</tbody>
</table>

**Abbreviations:** LD, learning disabilities; SLE, systemic lupus erythematosus.

* $P < .05$

† Defined as disease activity.

trous than sons of control mothers was similar to that of the one previous study, although not to that of the other related study. A positive relationship between nonright-handedness and LD has been documented in some developmental studies but not in others.

Results also showed that disease flare and presence of anti-Ro/La antibodies were associated with LD in sons. The measure for flare is a global one and takes into account a number of different medical variables. Therefore, the association between the presence of lupus disease activity (flare) and LD is less useful in postulating a causal link between maternal SLE and LD in boys than is the presence of anti-Ro/La antibodies. The relationship between the presence of maternal anti-Ro/La antibodies and subsequent LD in offspring has been proposed by previous and related work. However, to our knowledge, this is the first study to demonstrate a link between the presence of anti-Ro/La antibodies in pregnant women and later LD in their sons. The theory of maternal immunoreactivity posits that antigens associated with the Y chromosome cause mothers to produce antibodies that attack those antigens. These conditions result in a greater likelihood of maternal antibodies affecting the developing brains of male fetuses, with the subsequent expression of learning and other developmental disorders. Furthermore, the theorists argue that women with autoimmune or allergic disorders are more likely to have an immunoreactive response during pregnancy than are women without those conditions. Our results showed that sons of women with SLE are more likely to have LD, and also that mothers with SLE who have sons are more likely to have anti-Ro/La autoantibodies. As such, the study supports the immunoreactivity theory.

This research suggests the importance of controlling disease activity and lowering levels of maternal antiRo/La antibodies during pregnancy. At the present time, it is difficult to minimize disease flare and diminish the levels of maternal antibodies. In general, high doses of corticosteroids are required, and the potential risk for 9 months of high-dose corticosteroid therapy is significant and increases maternal and fetal morbidity. Thus, it is not feasible to control maternal disease activity and lower antibody levels in women with SLE during pregnancy as a potential means of reducing the prevalence of LD in their children. However, knowledge of the higher
Two previous studies linking maternal autoimmune disease during pregnancy and LD in male offspring relied mainly on questionnaires to parents and, therefore, may have had biased results. In addition, the studies provided no evidence of a means by which the mothers’ autoimmune disease could result in LD in their sons.

Our research confirms previous results linking autoimmune disease in mothers during pregnancy to learning problems in sons through actual test results in the children, rather than relying on parental report. In addition, this study included data on presence of maternal antibodies, maternal disease activity, and maternal use of corticosteroids during pregnancy. Those data enabled us to conclude that presence of anti-Ro/La antibodies and disease activity during pregnancy predicted LD in offspring of women with autoimmune disease.

What This Study Adds

Risk for LD among sons of women with SLE should lead to greater awareness among pediatricians, parents, and educational professionals and to early intervention for those children.

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