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Increased usage of special educational services by children born to mothers with systemic lupus erythematosus and antiphospholipid antibodies

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ABSTRACT

Introduction: Surveys of long-term health and developmental outcomes of children born to mothers with systemic lupus erythematosus (SLE) have suggested an increase in learning disabilities among these children. We performed this observational study to investigate the relationship between maternal autoantibodies and antiphospholipid antibody syndrome (APS) in maternal lupus patients and neurocognitive development among their offspring.

Methods: SLE mothers with at least one live birth postlupus diagnosis were enrolled. Data on maternal medical/obstetric history and children's perinatal/medical history were collected by structured interview and medical record reviews. The primary outcome was requirement for special educational (SE) services, a proxy for developmental delays. Multiple logistic regression modelling was used to examine associations between APS and autoantibodies with SE usage, accounting for SLE disease severity and potential confounders.

Results: Data on 38 mothers and 60 offspring were analysed: SE service usage was reported for 15 of 60 (25%) offspring. Maternal APS history was significantly associated with increased use of SE services among offspring, including after adjustment for lupus anticoagulant (LA) positivity and potential confounders (OR 5.5–9.4 for delays age ≥2; p<0.05). The presence of LA, but not other antiphospholipid antibodies, was also associated with increased SE services usage.

Conclusions: Maternal APS and LA were independently associated with increased usage of special educational services among offspring of women with SLE.

KEY MESSAGES

- This research adds to a growing body of evidence suggesting that children born to mothers with lupus, in this case those with maternal antiphospholipid antibodies, may be at increased risk for developmental delays.
- More research into screening for early childhood developmental delays in these children is warranted.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder for which females experience disproportionate risk, particular from the reproductive years onward.[1 2] SLE pregnancies are associated with increased risk of adverse obstetric outcomes including preterm labour and pre-eclampsia.[3] The presence of antiphospholipid antibodies (aPL) and/or a history of renal disease or hypertension are known to affect the course of lupus pregnancies as well.[4–8] aPLs are associated with recurrent fetal loss and pre-eclampsia,[8] and are reported among a substantial proportion of SLE patients: approximately 30% of lupus patients are estimated to have the lupus anticoagulant (LA), 23–48% anticardiolipin antibodies, and 20% anti-β2-glycoprotein antibodies.[9 10]

Most studies published about lupus pregnancies have focused on obstetric and neonatal outcomes of offspring. As improvements in diagnosis and management over the last several decades have allowed more women with lupus the opportunity to achieve successful pregnancies,[11] there has been growing interest in the long-term outcomes of children born to mothers with SLE, including any neuropsychological and cognitive outcomes that may be impacted by SLE and its treatment during pregnancy. Growing evidence suggests increased rates of learning delays among offspring of mothers with SLE,[12–17] and associations between autism spectrum disorders, dyslexia and other neurocognitive dysfunction and specific maternal autoantibodies (anti-Ro, anti-La, aPLs).[18–22] We performed this study in

order to further investigate the relationship between antiphospholipid antibodies in a cohort of women with lupus, and neurocognitive development among their offspring.

METHODS

Study population

This study included women attending rheumatology outpatient clinics at the University of Michigan Health System, including patients enrolled in the Michigan Lupus Cohort. As described in more detail elsewhere,[14] study enrolment took place over the calendar period December 2008 to November 2010. SLE patients were eligible if they met ≥4 American College of Rheumatology (ACR) criteria for SLE [23 24] prior to at least one pregnancy, and had at least one live birth following SLE diagnosis. This research was approved by the University of Michigan Institutional Review Board. Written informed consent was obtained from participating mothers; assent or consent was obtained from the offspring for children aged 10–17 years old.

Data collection

Maternal history

Data were collected from the mothers during an interview with a maternal fetal medicine investigator, using a structured format that included medical and obstetric history. Data elements included maternal medical history, including details of SLE history, such as associated manifestations and organ involvement. Data were also collected on general historical medical information, including history of hypertension or cardiovascular events. A detailed history of medication exposures during pregnancy was obtained. Laboratory data, including results of renal biopsies, if applicable, were also recorded.

Antiphospholipid antibodies and syndrome

History of antiphospholipid antibody syndrome (APS) was defined according to the Sydney classification criteria developed by expert consensus agreement in 2006,[25] which represented an updated version of the Sapporo criteria for APS developed in 1999.[26] Individual antiphospholipid antibodies were recorded, as described below. IgG and IgM isotypes of anticardiolipin (aCL), and β-2-glycoprotein 1 (β2GP1), were classified as positive if greater than the 99th percentile at our institution, on two or more occasions, at least 12 weeks apart, prior to, or during the study pregnancy, which corresponded to the following cut-offs: aCL IgG (≥22 GPL); aCL IgM (≥25 MPL); β2GP1 IgG (≥24 U/mL); β2GP1 IgM (≥26 U/ML). The LA was identified either by prolongation of activated partial thromboplastin time or dilute Russell's viper-venom time (dRVVT) with a positive confirmatory test.

Offspring history

Medical and developmental histories of the offspring of the maternal participants were performed, including antenatal, delivery, perinatal and paediatric histories, as described elsewhere.[14] The study instrument (questionnaire) was, in part, designed to capture data on perinatal and early life health up to age 2 years, so data collection was categorised by age <2 years, or 2 years and above. Briefly, our primary outcome measure was usage of special educational (SE) services, based on maternal report of recommendation by a physician or educator due to concern for delay in a child's cognitive, physical or social maturity compared with established age-appropriate norms. Speech or hearing delays, diagnosis of attention-deficit hyperactivity disorder (ADHD), or any special educational need prompting a teacher or paediatrician to initiate referral for SE services (eg, occupational or speech therapy, behavioural counselling, tutoring) were recorded. Referrals were categorised according to whether they occurred at any age, during the first 2 years of life, and/or from age 2 years onward.

Statistical analysis

Baseline summary statistics were computed as mean and SD for continuous variables, or frequency and proportion for categorical variables. Variables were assessed for normality, and non-parametric statistics were used if appropriate. Demographic characteristics of mothers among the groups with and without SE services usage were checked for comparability. The outcomes were examined based on four categories of possible education needs: any need, need for service prior to age two, after age two, or speech delay. We tested baseline characteristics of the offspring (maternal antibody profile, maternal SLE duration, maternal hypertension, pregnancy complications, gestational age, birth weight, congenital heart block, and sex of child) among those children with and without each educational need type using Fisher's exact test and the Wilcoxon rank-sum test. Using logistic regression, we computed ORs and 95% CIs to examine the association between maternal APS or the presence of antiphospholipid antibodies and referral or need for SE services.

To adjust for other covariates, we used standard and exact multivariable logistic regression; due to the limited sample size, separate bivariate models were used to adjust for covariates of interest, since models with more than two covariates would be unstable. Model fit was assessed using the Hosmer–Lemeshow test. In order to account for potential correlation due to multiple births from some mothers, we also fit models using a reduced sample consisting of only one randomly selected child from each mother, and conducted a simulation of 1000 permutations of mother–child combinations in order to examine the distribution of p values from these models. All statistical analyses were performed in Stata V.11.1.[27]

RESULTS AND DISCUSSION

Eighty-five women were screened for participation in the study, of whom 38 met eligibility criteria and enrolled in

Table 1 Maternal characteristics among mothers with SLE (n=38)

Characteristic	n (%) or median (IQR)
Maternal race	
African–American	5 (13)
Caucasian	25 (66)
Asian	3 (8)
Other	5 (13)
Marital status	
Married	32 (84)
Divorced/single/separated	6 (16)
Maternal education (years)	16 (16, 18)
Country of birth	
USA	34 (89)
Other	4 (11)
Number of pregnancies	2 (2, 3)
Number of children	2 (1, 2)
SLE features*	
Antiphospholipid antibody syndrome (APS)	7 (18)
Malar rash	24 (63)
Discoid rash	3 (8)
Photosensitivity	24 (63)
Oral ulcers	18 (47)
Arthritis	36 (95)
Serositis	15 (39)
Renal disorder	17 (45)
WHO class ≥ III	12 (32)
Neurological disorder	11 (29)
Hematological disorder	23 (61)
Immunological disorder	31 (82)
Antinuclear antibody	34 (89)

*SLE features defined according to ACR classification for SLE, except for APS which was according to Sydney criteria.

this study. Among these 38 mothers, 60 eligible offspring were included. The mean age range of the children at the time of data collection was 6.6 years (SD±3.8). Maternal characteristics of the study participants are summarised in table 1. We did not find significant differences in maternal characteristics, including race, age, or educational level, between the mothers of the children who were referred for SE services compared to those who were not. Among the offspring included in this analysis, there were 56 singleton births, and 2 sets of twins. There was no usage of SE services reported for the children of the twin pregnancies. Of the 60 children, 62% were female, 6 (10%) were born at gestational age of less than 32 weeks, 17 (28%) between 32 and 37 weeks, and 15 (25%) were small for gestational age. There was one case of congenital heart block without any special educational needs.

SE services usage overall occurred in 15 (25%) of the 60 children. The most prevalent type of educational need was for speech delay requiring speech therapy in 12 (20%) of the children in this study. Attention-deficit disorder was reported for 3 (5%) of the 60 children. When categorised according to age of intervention, 10 of 60 (17%) children were referred in the first 2 years of life, and 14 (23%) from age 2 years onward, with 9 children referred in both age categories.

We explored several factors that had been previously suspected to be associated with developmental delays. We did not detect associations between maternal clinical features, such as SLE disease duration, lupus nephritis or flare during pregnancy, or pre-eclampsia. Likewise, gestational age, birth weight, and small for gestational age, were not detected to be associated with SE usage. Investigation of autoantibodies (table 2) revealed that maternal APS and LA positivity were each significantly associated with need for SE services: APS was significantly associated with any delay (p=0.04) and delays ≥2 years (p=0.01). Among particular antiphospholipid antibodies, LA was significantly associated with delays at <2 years (p=0.01), whereas aCLs and anti-β2GP1 were not detected to be associated with delays.

We further investigated the association between APS and SE usage using logistic regression modelling (table 3). Crude ORs were 5.1 (95% CI 1.2 to 22.6) for the association with any use of SE services, and 7.8 (95% CI 1.6 to 38.6) for the association with usage from age 2 years onward. Magnitudes of association remained similar for bivariate models adjusting for pregnancy duration, small for gestational age, and maternal education. There were not enough cases of SE services usage in the first 2 years to model those outcomes in multivariable models. In order to account for potential correlation between offspring of the same mother, we did a simulation of 1000 permutations of mother–child combinations using exact logistic regression. For the association between APS and SE services needs, 14.8% of the 1000 random samples had associated p values of <0.05, and 24.6% generated a p value of <0.10, supporting the conclusions from the models that included all 60 offspring.

When simultaneously modelling APS and LA positivity, positive associations between APS and SE services usage persisted, though slightly lower in magnitude—OR 3.8 (95% CI 0.8 to 18.1) for any delay and 5.5 (95% CI 1.1 to 28.7) for delays age 2 years onward. The stability in effect estimates for SE services categorised as any delay or delays from age 2 years onward supports an independent association between APS and SE services needs even after accounting for LA positivity.

We controlled for multiple potential confounders, including accounting for underlying disease severity by using propensity scoring, and controlling for variables related to lupus disease activity, perinatal complications (including intrauterine growth restriction), and effects of various medications commonly used in treating SLE and APS during pregnancy. One of these medications, injectable heparin, is indicated for treatment of pregnant women with APS, so we therefore explored whether the APS association was modified by this variable. Overall, five of the mothers were taking heparin during pregnancy, of whom two were mothers with secondary APS. There was no association between heparin and SE services usage

Table 2 Special educational (SE) service needs corresponding to maternal autoantibodies and antiphospholipid antibody syndrome

	No SE services	SE services		
	Referent (n=45)	Any (n=15)	Age <2 (n=10)	Age ≥2 (n=14)
Autoantibody features				
APS	4 (9)	5 (33)*	3 (30)	5 (36)**
aPLs				
LA	16 (36)	11 (73)	9 (90)**	10 (71)
aCL—IgG	9	6	5	5
aCL—IgM	0	0	0	0
anti-β2GPI—IgG	0	0	0	0
anti-β2GPI—IgM	1	0	0	0
Anti-Ro/SSA	16 (36)	3 (20)	2 (20)	2 (14)
Anti-Ro among APS+	1 (2)	1 (7)	0 (0)	1 (7)
Anti-La/SSB	8 (18)	1 (7)	0 (0)	1 (7)
Anti-La among APS+	2 (4)	1 (7)	0 (0)	1 (7)
Propensity Score†	0.12 (0.19–0.15)	0.16 (0.10–0.30)*	0.16 (0.09–0.17)	0.18 (0.12–0.30)**

Data are presented as frequency (%) for categorical variables or median (IQR) for continuous variables.
*p<0.05;
**p≤0.01.
†Propensity score (for APS) uses non-fluorinated steroids, WHO class III and up for renal biopsy, and flare during pregnancy.

based on univariate modelling in the offspring of these women, and when adjusted for heparin used, the APS association with SE services was similar to the crude estimate. Another medication used frequently during lupus pregnancies is azathioprine, and we previously demonstrated in this study population that in utero azathioprine exposure was associated with increased usage of SE services.[14] We therefore adjusted for azathioprine use during pregnancy, and maternal APS remained significantly associated with need for SE services.

CONCLUSIONS

In this study of 60 children born to mothers with lupus, maternal APS was associated with a threefold to eightfold increase (depending on the category of delay and other covariates included in the modelling) in the requirement for special educational (SE) services, a proxy for developmental delays in offspring. The association between maternal APS and need for SE services was robust across models, including after adjustment for recognised risk factors for future learning disorders, particularly prematurity and low birth weight.[28 29] The population we studied included women with a wide range of lupus disease activity during pregnancy, and a substantial number with a history of lupus nephritis and extrarenal lupus, many of whom had sufficient disease activity to require immunosuppressive therapy during their pregnancy. However, maternal lupus disease activity and other maternal factors including pre-eclampsia, history of hypertension, or lupus nephritis prior to pregnancy did not

Table 3 Association between maternal antiphospholipid antibody syndrome (APS) and special educational (SE) services requirement among offspring

Covariates	Any SE service (n=15) OR (95% CI)	SE service age ≥2 years (n=14) OR (95% CI)
APS (crude)	5.1 (1.2 to 22.6)*	7.8 (1.6 to 38.6)*
APS adjusted for:		
+Pregnancy duration (weeks)	4.1 (0.9 to 19.3)	6.7 (1.3 to 35.2)*
+Small for gestational age	5.0 (1.1 to 22.3)*	7.6 (1.5 to 38.3)*
+Maternal education (years)	4.3 (0.9 to 19.8)	7.5 (1.4 to 39.1)*
+Lupus anticoagulant	3.8 (0.8 to 18.1)	5.5 (1.1 to 28.7)*
+Heparin	4.0 (0.9 to 18.5)	6.8 (1.3 to 35.1)*
+Pscore +AZA	4.2 (0.82 to 21.7)	9.4 (1.47 to 60.0)*
Lupus anticoagulant (crude)	4.0 (1.1 to 14.7)*	3.2 (0.9 to 12.1)
+APS	3.6 (0.9 to 13.8)	2.6 (0.7 to 10.5)

ORs represent the effect estimates for APS based on the crude (univariate) logistic regression models and additional bivariate logistic regression models adjusted for the covariates listed.
*Indicates statistical significance (p<0.05).
APS, antiphospholipid antibody syndrome; DD, developmental delay.

predict which children were more likely to be referred for SE services, raising the question of whether aPLs themselves affect fetal neurocognitive development, much as maternal anti-Ro/SSA and anti-La, SSB antibodies target the antigenic cells in the fetal conduction system.[20 30]

We examined the association of different classes of aPLs with the need for SE services, and found that the presence of LA, but not aCLs or anti-β2GP1 antibodies, was associated with an increased need for SE services in offspring; 90% of children in this study under age 2 years requiring SE services were born to mothers who were LA positive. A potential mechanism for a heightened association between LA and usage of SE services (beyond the other aPL subgroups) is unclear. However, LA has been shown to have greater clinical relevance than aCLs in predicting venous thrombosis in SLE patients.[31] Furthermore, recently published results from the Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus (PROMISSE) study revealed a significant association between LA (but not the other classes of aPLs) with adverse pregnancy outcomes, including unexplained fetal death.[32] However, triple aPL positivity (LA, β2GP1, and anticardiolipin antibodies) in association with a history of thrombosis has been suggested to be a stronger predictor of adverse pregnancy outcomes than positivity for any individual aPL.[33]

Our findings of maternal APS and LA positivity as significant predictors of SE service usage in offspring support other studies of adverse neurodevelopmental outcomes in offspring born to mothers with SLE as well as APS.[13 15 22 30] In one study in which standardised, age-appropriate intelligence and performance tests were administered to 47 children born to mothers with SLE, investigators found that the children had normal IQ scores, but those who had low scores in specific tests were significantly more likely to be born to mothers who were positive for aPLs (3/3 vs 2/11; p=0.02), although the particular subtype of aPL was not stated.[22] A 2008 study in which children born to mothers with primary APS were evaluated using standardised tests of intelligence and cognitive abilities, found learning disability in 4 of 15 children, though complications, such as prematurity and low birth weight were not controlled for.[21] A prospective European registry following a cohort of children born to mothers with APS (by Sapporo criteria) reported follow-up from birth to age 5 years of 141 children in which 4 children born to mothers with primary obstetric APS had clinical features of autism and hyperactive behaviour (in 2 children), feeding disorders, language delay, and growth failure (in 1 child), axial hypotony (in 2 children) and psychomotor delay (in 1 child).[34] Results are inconsistent regarding learning or developmental delays in children born to mothers with anti-Ro and anti-La antibodies.[20] We did not find any relationship between the presence of anti-Ro or anti-La antibodies and increased rates of usageof SE services in our study, nor did we find differential risks for male compared to female offspring.

While our study did not include an external control group, the Citizen's Research Council of Michigan[35] estimates that approximately 14% K-12 students in the state received special education services in 2010, a level which is approximately half of what we observed in children born to SLE mothers in our study population. Furthermore, the most common category identified for SE needs in children from the general Michigan population was for specific learning disability and speech/language impairment (60%); by comparison, we noted a higher percentage of children in our study (12/15 (80%)) with a speech delay requiring speech therapy.

Our study is somewhat limited because the data were acquired retrospectively, and the mothers' recollections of requirements for SE services or any associated developmental delays in their children could have resulted in recall bias. However, we would not expect that APS in the context of a complex disease such as lupus would influence recollection one way or another. We were not able to directly account for correlations between siblings from the same mother due to small sample size, so instead, we used a separate model which randomly selected for one child from each mother, but further reduced the sample size. We also observed that children with a SE need in their first 2 years of life were more likely to have ADHD or further SE needs as older children, so these children were included in both age categorisations of delays, resulting in a large degree of overlap and significance across multiple categorisations for a given characteristic. Finally, because this was a hypothesis-generating observational study, outcomes were not based on standardised neurocognitive testing. Future research incorporating formal neurocognitive testing is needed in order to more fully characterise the extent and predictors of developmental delays in this population.

Strengths of our study include a population from a well-characterised cohort of women with a wide range of lupus disease activity, a significant number of whom required immunosuppressive, antimalarial and/or glucocorticoid therapy during their pregnancies. Because the patients enrolled in this study were followed at the University of Michigan, all laboratory assays were standardised. The multidisciplinary research team involved in this study consisted of rheumatologists and a maternal fetal medicine specialist, whose extensive experience of high-risk pregnancies allowed for the capture of accurate data relating to the prenatal and perinatal periods. Finally, we used a maternal report of SE usageas a proxy variable for developmental delay in offspring, and consider it to be a clinically relevant endpoint, prompting intervention from a healthcare or educational provider.

This pilot study of long-term outcomes of children born to mothers with lupus is consistent with a growing body of literature supporting a potentially pathologic association of transplacental maternal antiphospholipid autoantibodies and impaired neurocognitive development in offspring. These findings should raise the index

of suspicion among paediatricians and rheumatologists caring for these mothers and children, and prompt appropriate referral for assessment of neuropsychiatric function. There is increasing recognition that early identification, intervention and treatment, even during infancy, can improve long-term function in children with developmental delays.[36] Future directions of this research should include elucidation of mechanistic processes associated with antiphospholipid antibodies, and their effects on fetal neurodevelopment.

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