Atrioventricular Conduction in Children of Women with Systemic Lupus Erythematosus

Monica Martin Goble, MD, Macdonald Dick II, MD, W. Joseph McCune, MD, Janet Ellsworth, MD, Donita B. Sullivan, MD, and Aaron M. Stern, MD

The neonatal lupus syndrome consists of transient cutaneous lupus lesions or permanent congenital complete heart block (or hepatic fibrosis), or both, in infants born to mothers with systemic lupus erythematosus (SLE). The frequency of conduction abnormalities was examined in 86 offspring of 53 women affected by SLE. Electrocardiograms from the offspring demonstrated normal sinus rhythm in 84 of 86 offspring. The PR interval was normal for age (<95th percentile) in 82 offspring and normal for heart rate in 81. Three children had a PR interval >95th percentile (i.e., first-degree heart block) for both age and heart rate. The PR interval of the other 6 subjects with first-degree heart block for age or heart rate (≥95th percentile) was ≤0.18 second. In contrast, using a rank assignment of PR intervals in relation to heart rate and age derived from published standards, grouped data indicated that heart rate adjusted for age was greater and PR interval adjusted for heart rate longer in offspring of mothers who had the onset of SLE before or during pregnancy than in the normal population; this observation did not hold for offspring whose mothers developed SLE after the pregnancy. These findings indicate that offspring of mothers with SLE, even in the absence of an abnormal electrocardiogram, may have experienced a maternal internal environment that produces subclinical changes in atrioventricular conduction. However, newborns with a normal pulse rate are unlikely to have significant abnormalities in atrioventricular conduction and do not need screening electrocardiograms at birth.

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The neonatal lupus syndrome consists of transient cutaneous lupus lesions or permanent congenital complete heart block (or hepatic fibrosis), or both, occurring in a small percentage of infants born to mothers with systemic lupus erythematosus (SLE). The prevalence of connective tissue disease in mothers of babies with congenital complete heart block ranges from 33 to 64%.[1,2] Half of these women are symptomatic; the other half have only serologic evidence of connective tissue disease.[3] In symptomatic mothers, SLE is the usual underlying disorder, but Sjogren syndrome, rheumatoid arthritis and undifferentiated connective tissue disease have also been found.[2,4,5] In 1 study, the relation between maternal high-titer antibody and congenital complete heart block suggested a possible dose-response effect.[6] However, the electrocardiograms of all the infants were not reported. Support for a dose-response relation would be increased, if more subtle conduction disturbances were detected by the electrocardiogram. This study examines the frequency of conduction abnormalities in offspring of mothers with SLE by identifying mothers with SLE rather than by identifying affected infants. Our hypothesis is that offspring of mothers with SLE would have a spectrum of conduction disturbances on the resting electrocardiogram ranging from first-degree atrioventricular block to the already recognized congenital complete heart block.

METHODS

In 1982 and again in 1988, women with SLE (1982 American Rheumatism Association revised criteria for SLE) followed in the Rheumatology Clinic at the University of Michigan were asked at the time of their regularly scheduled appointment if they had ever been pregnant. For each cohort (1982 [n = 32] and 1988 [n = 21]), women with children were later contacted by telephone and asked to participate in the study. Thirty-two of 42 mothers contacted in 1982 and 21 of 22 in 1988 agreed to participate in the study. In all, 84 of 92 living offspring of 53 women were evaluated. Except for 3 siblings who had electrocardiograms obtained at a local hospital, electrocardiograms were recorded on a Cambridge VS-550 electrocardiographic recorder (frequency response, direct current to 100 Hz) with a heat writer on paper moving at 50 mm/s. Consent forms and questionnaires pertaining to the mother's and child's medical history were completed for each offspring. Anti-SSA/Ro and Anti-SSb/La antibody status was available from 25 mothers (18 from 1988, and 7 from 1982). The study protocol, written

From the Divisions of Pediatric Cardiology and Pediatric Rheumatology, Department of Pediatrics, and the Division of Rheumatology, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan. Dr. Goble is now at the Medical College of Virginia, Richmond, Virginia. This study was supported in part by Grant M01-RR00042 from the National Institutes of Health, Bethesda, Maryland. Manuscript received May 26, 1992; revised manuscript received and accepted July 27, 1992.

Address for reprints: Macdonald Dick II, MD, F1310 Box 0204, C.S. Mott Children's Hospital, University of Michigan Medical Center, 1500 East Medical Center Drive, Ann Arbor, Michigan 48109-0204.

consent forms and questionnaires for both cohorts were similar and were approved by the institutional review board of the University of Michigan.

Electrocardiographic intervals (Table I) (heart rate, and PR, QRS and QT intervals) were measured independently by 2 investigators using a ruler calibrated to 0.5 mm. Because electrocardiographic standards for children have been published, are widely accepted and are constant over time, a contemporary control group was not necessary. We used standards published in 1980 by Davignon et al[7] that were derived from data in a population of 2,141 children (age range 0 to 16 years) divided into 12 age groups. Age-dependent PR intervals and QRS duration percentiles, as well as distributions of

TABLE I Maternal Antibody Status and Offspring Electrocardiographic Data

						Electrocardiographic Intervals		
Mother	Ro-Ab	La-Ab	Offspring	Age (year)	HR (beats/min)	PR (ms)	QRS (ms)	QTNC (ms)
1	Neg	Neg	1A	14	91	130	70	340
			1B	11	92	160	80	320
2	Pos	Pos	2	17	85	120	80	320
3	Neg	Neg	3	2	115	110	80	280
4	Neg	Neg	4	3	101	160	80	320*
5	Pos	Pos	5	16	107	120	60	300
6	Pos	Neg	6	8	81	120	70	350
7	Pos	Neg	7	24	79	140	80	340
8	NA	NA	8	6	107	100	60	320
9	NA	NA	9A	12	64	160	80	340
			9B	15	58	160	100	400
			9C	14	58	90	100	440†
10	Neg	Neg	10A	6	100	170	100	300‡
			10B	9	65	130	60	340
			10C	12	75	150	70	360
11	Neg	Neg	11	6	97	120	80	320
12	Neg	Neg	12	6	64	120	80	360
13	Pos	Neg	13	3	143	130	60	260
14	Pos	Pos	14	15	65	140	80	360
15	Pos	Neg	15A	13	71	160	40	330
			15B	6	95	150	60	320
16	Neg	Neg	16	2	140	120	50	260
17	Neg	Neg	17	0.5	136	170	50	300‡
18	NA	NA	18A	28	98	160	70	330*
			18B	36	85	180	80	330*
			18C	39	88	160	60	360
19	Neg	Neg	19	13	79	140	80	350
20	Pos	Neg	20	6	89	110	50	300
21	Pos	Pos	21A	10	100	120	80	320
			22B	0.3	118	80	50	300§
22	NA	NA	22A	13	77	160	70	320
	NA	NA	22B	15	95	140	80	340
23	NA	NA	23	0.11	165	110	40	220
24	Neg	Neg	24	0.13	200	80	40	220
25	NA	NA	25A	13	83	140	60	360
			25B	20	75	140	100	370
26	NA	NA	26	4	75	120	60	320
27	NA	NA	27	3	100	140	80	320
28	NA	NA	28A	4	95	140	70	300
	NA	NA	28B	12	82	120	70	370
	NA	NA	28C	17	67	140	60	360
	NA	NA	28D	21	78	150	60	340
29	Neg	Neg	29A	15	70	150	90	380
	Neg	Neg	29B	12	67	130	80	400
	Neg	Neg	29C	9	65	160	80	380
30	NA	NA	30A	10	75	120	60	320
	NA	NA	30B	5	80	120	60	320
31	NA	NA	31A	11	60	120	70	380
32	Neg	Neg	32A	15	73	160	90	360
	Neg	Neg	32B	13	69	180	80	370‡
33	NA	NA	33A	11	105	130	60	300
	NA	NA	33B	10	67	140	60	370
	NA	NA	33C	9	107	120	70	300

*First-degree heart block for age or heart rate; †atrioventricular dissociation with junctional rhythm; ‡first-degree atrioventricular block for both age and heart rate; §short PR interval with no δ wave, suggesting enhanced atrioventricular conduction.

HR = heart rate; La-Ab = anti-La antibody; NA = not available; Neg = maternal antibody not detectable; Pos = maternal antibody present; PR = PR interval; Ro-Ab = anti-Ro antibody.

TABLE I (Cont'd)

Mother	Ro-Ab	La-Ab	Offspring	Age (year)	HR (beats/min)	Electrocardiographic Intervals		
						PR (ms)	QRS (ms)	QTNC (ms)
34	NA	NA	34A	22	60	160	80	360
	NA	NA	34B	26	75	180	60	360*
	NA	NA	34C	31	49	160	100	380
	NA	NA	34D	28	77	140	80	400
35	NA	NA	35A	14	75	140	60	360
	NA	NA	35B	7	80	120	80	360
36	NA	NA	36	24	74	160	80	400
37	NA	37A	36A	15	75	140	100	370
		37B	36B	14	75	160	100	330
38	NA	NA	38	7	72	120	60	300
39	NA	NA	39A	33	63	160	80	360
	NA	NA	39B	30	72	140	80	360
	NA	NA	39C	24	75	140	90	320
40	NA	NA	40	7	136	150	80	260
41	NA	NA	41A	20	86	150	70	330
	NA	NA	41B	23	63	160	60	340
	NA	NA	41C	25	88	140	50	320
42	Pos	Neg	42	31	75	160	80	370
43	Neg	Neg	43A	5	88	140	80	340
	Neg	Neg	43B	10	88	120	60	340
44	NA	NA	44	10	100	140	60	320
45	NA	NA	45	42	75	100	60	370
46	NA	NA	46A	11	70	120	80	380
	NA	NA	46B	12	68	120	60	400
47	Pos	Neg	47	14	96	140	80	360
48	NA	NA	48	32	70	150	60	340
49	Pos	Neg	49	28	77	140	70	360
50	NA	NA	50	12	114	160	60	310
51	NA	NA	51A	28	68	120	60	360
	NA	NA	51B	25	60	180	70	440
52	NA	NA	52A	14	75	130	90	320
	NA	NA	52B	17	53	160	90	380
53	NA	NA	53	20	100	140	70	320

*First-degree heart block for age or heart rate; †atrioventricular dissociation with junctional rhythm; ‡first-degree atrioventricular block for both age and heart rate; §short PR interval with no δ wave, suggesting enhanced atrioventricular conduction.
HR = heart rate; La-Ab = anti-La antibody; NA = not available; Neg = maternal antibody not detectable; Pos = maternal antibody present; PR = PR interval; Ro-Ab = anti-Ro antibody.

these values, from that study were used as the normative values in the present study. However, because of the wide range of normal PR intervals at different heart rates and ages (Figures 3 and 4 from Davignon et al),[7] each PR interval of the subjects in our study was assigned a rank order of 1 to 8 corresponding, in order, to a rank value <2nd percentile (rank value = 1), between the 2nd and 5th, the 5th and 25th, the 25th and 50th, the 50th and 75th, the 75th and 95th, and the 95th and 98th percentiles, and finally, >98th percentile (rank value = 8). The following 3 analyses were then performed: (1) comparison of the 1982 and 1988 data to determine if the cohorts differed; (2) comparison of all data to examine the effect of onset (before and during vs after pregnancy), as well as other variables; and (3) repetition of analysis 2 using only data from the eldest child to eliminate any intrafamily effects. Tests used to perform these analyses included 1-way analysis of variance model, Mann-Whitney nonparametric test, chi-square test of independence, and analysis of co-variance and log-linear models. Differences were considered significant if the p value was ≤ 0.05.

RESULTS

In this group of 53 women with SLE, serologic results were known for 25 (Table I). A woman was considered as having anti-SSA/Ro antibody if the antibody was found at any time. The rationale for this assumption is based on the reported occurrence of anti-SSA/Ro antibody before the onset of symptoms of SLE[3] and because this antibody tends to remain present over prolonged periods of time.[8] Of these 25 women, most (76%) were antinuclear antibody positive; 50% were anti-SSA/Ro antibody positive, and 56% were anti-SSB/La antibody positive. No mother had a child with congenital complete heart block.

The mean age of the offspring studied was 14.5 ± 9.5 years. One-way analysis showed that the 1982 cohort was older ($p = 0.05$) and, as would thus be expected, had a slower heart rate ($p = 0.04$) than did the 1988 cohort. However, the electrocardiographic intervals did not differ significantly between the 2 groups. SLE was diagnosed before or during pregnancy in 28 cases and after pregnancy in the remaining 58. During 7 pregnancies, the mothers were treated with prednisone.

Analysis of electrocardiographic data (Table I) showed sinus rhythm in 85 of 86 offspring. A 14-year-old male offspring had both intermittent atrioventricular dissociation and normal sinus rhythm, but normal atrioventricular conduction during sinus rhythm. Serologic data were not available from this subject's mother. One 20-year-old female offspring had right-axis deviation. The PR interval was <95th percentile for age (i.e., normal) in 82 of 86 offspring and <95th percentile for heart rate in 81. Three children had a PR interval >95th percentile (i.e., first-degree heart block) for both age and heart rate: A 6-month-old male had a PR interval of 0.17 seconds at a heart rate of 136 beats/min, a 6-year-old male had a PR interval of 0.17 second at a heart rate of 100 beats/min, and a 13-year-old male had a PR of 0.18 second at a heart rate of 69 beats/min. Although 2 of the mothers of these 3 subjects developed SLE before or during the pregnancy, all 3 mothers' serum was devoid of anti-SSA/Ro and anti-SSB/La antibody. The PR interval of the other 6 subjects with first-degree heart block for age or heart rate (i.e., ≥95th percentile) was ≤0.18 second. However, all offspring had intact atrioventricular conduction, and no other isolated electrocardiographic abnormalities were found.

In contrast to the individual data, grouped data suggested subtle effects of maternal SLE on atrioventricular conduction in offspring. Using the aforementioned rank assignment of PR intervals in relation to heart rate and age (and heart rate in relation to age), 2 differences were observed. First, heart rate adjusted for age was significantly ($p = 0.003$) higher in offspring whose mothers had the onset of SLE before or during pregnancy than in the normal population[7]; this difference was not present for children whose mothers developed SLE after pregnancy. Second, PR interval adjusted for heart rate (i.e., rank score indicating a difference in percentile level) was significantly ($p = 0.0001$) longer (i.e., score was greater) in offspring whose mothers developed SLE before or during pregnancy than in the normal population.[7] This difference was not present for subjects whose mothers developed SLE after pregnancy. These relations remained when only the eldest child was included in the analysis, supporting the likelihood of a difference related to SLE effects rather than to intrafamily effects. However, the data were insufficient to distinguish between the effects of age and onset of SLE (before and during vs after pregnancy) on PR interval. The analysis examining an antibody effect on PR interval produced no significant results, perhaps owing to a small number of women in whom antibody status was known.

DISCUSSION

In these 2 cohorts comprising 86 offspring of 53 mothers with SLE, we detected no isolated, significant, electrocardiographic abnormalities, even in children whose mothers were anti-SSA/Ro antibody positive. First-degree atrioventricular block was detected in 3 offspring; however, the 3 respective mothers were antibody negative during pregnancy, suggesting that in these cases the minor conduction abnormalities were probably unrelated to neonatal SLE. Similarly, the finding of an intermittent escape junctional rhythm in 1 adolescent offspring, as well as the right-axis deviation in another, probably represents a normal variant. However, the grouped data suggest that a subclinical effect of maternal SLE may be affecting the fetus and may contribute to a subtle delay in atrioventricular conduction in the fully developed infant or child.

Mechanism of neonatal systemic lupus erythematosus: Neonatal SLE syndrome is mediated by the transplacental passage (after the 12th to 16th week of gestation) of maternal immunoglobulin G antibodies to the fetus of a woman with SLE, followed by an immunologically-based inflammatory reaction (and/or deposition) of these antibodies with antigens of the fetal skin and heart, or both.[3,5,6,9–14] Anti-SSA/Ro and anti-SSB/La antibodies to soluble tissue ribonucleoprotein antigens found in the cytoplasm or nucleus of human cells, or both,[10] have been proposed as the etiologic agents of congenital complete heart block.[11] Demonstration of immunofluorescence from antibody deposition in cardiac tissue provides evidence that placentally transmitted immunoglobulin G antibodies may act directly on the heart, producing deposition at the atrioventricular node, central fibrous body and fibrous annulus.[15–19] Furthermore, Alexander et al[20] have demonstrated an antibody (anti-SSA/Ro and anti-SSB/La)-mediated inhibition of neonatal rabbit cardiac repolarization, indicating a direct effect on the electrophysiologic properties of developing excitable tissue. All these observations are compatible with a dose-response effect of maternal antibodies on immature atrioventricular conduction tissue.

Risk to fetus: In a retrospective study of offspring of women with SLE, Ramsey-Goldman et al[6] described 16 infants with congenital complete heart block in 96 pregnancies of women who had anti-SSA/Ro antibody. In contrast, only 1 infant in 235 pregnancies of women with SLE but without anti-SSA/Ro antibody had neonatal SLE. In that study, the overall risk of a woman with SLE having an infant with congenital complete heart block was estimated to be 1:60 (when corrected for referral bias), but the risk was considerably greater (1:20) if anti-SSA/Ro antibody was present. Buyon et al[21] have described maternal antibodies from the mothers of neonatal SLE infants to specific peptides of the ribonuclear SSA/Ro complex, as well as to the SSB/La particle; both of these peptides are abundant in fetal cardiac tissues. The presence of antibodies to these specific peptides increases the risk ratio of a mother with SLE giving birth to an infant with neonatal lupus by a factor of 35.

Clinical implications: The incidence, reduced morbidity and improved survival of women of childbearing age affected by SLE renders pregnancy in these cases an important clinical problem. This study was retrospective. Thus, transient conduction disturbances in the neonatal period may have been overlooked. However, the study underscores the strong possibility of subclinical alterations in atrioventricular conduction in some fetuses exposed to a maternal SLE environment, and thus supports a dose-response relation between atrioventricular conduction in the fetus and infant and maternal SLE

antibodies. However, because of bradycardia noted in the newborn at birth, congenital high-grade or complete heart block is usually recognized and confirmed by electrocardiography. Thus, if the heart rate of a fetus or newborn whose mother has SLE is normal, neither early obstetric intervention nor routine postnatal electrocardiograms are necessary.

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