PAPERS AND ORIGINALS

Congenital heart block and maternal systemic lupus erythematosus

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Summary and conclusions

The association between infants with congenital heart block (CHB) and the presence or later development of maternal systemic lupus erythematosus or other connective-tissue disease (CTD) was reviewed in 67 cases. In 24 cases CHB was diagnosed at or before birth. Of nine necropsies on affected infants, seven showed endomyocardial fibrosis. The results suggest that one in three mothers who deliver babies with CHB have or will develop CTD.

The association is probably explained by placental transfer of a maternal antibody. Awareness of the association may lead to prevention of the birth of children with CHB and better neonatal care of affected children.

Introduction

Complete congenital heart block (CHB) occurs in only about 1 in 20 000 pregnancies.[1] About a quarter of the cases are associated with a heart malformation, but in the remainder the aetiology is unknown. Pregnancy in women with systemic lupus erythematosus (SLE) is also rare, occurring in about 1 in 1500.[2 3] In 1976 we discussed a case in which congenital heart block and maternal SLE were associated in relation to two others recorded, certain features suggesting that the association was not fortuitous.[4] Since then at least 30 cases have been reported and we have traced a further eight earlier case reports. It now appears that SLE is of major importance in the aetiology of CHB and that the relation extends to other connective-tissue diseases (CTD). The association is also relevant to the pathogenesis of CTD. We have reviewed the evidence based on a series of 27 cases recorded here and 40 cases documented by other workers.

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Methods and results

Our 27 cases comprised 23 from Scandinavia and four from the United Kingdom, most of which were entered in the co-operative study of CHB organised by the Association of European Paediatric Cardiologists (AEPC). Information on mothers who had borne children with CHB was obtained in several ways. AEPC study records on 583 cases were reviewed for a history of maternal CTD given at the time of entry; of these, 10 were positive. Current histories with specific inquiry about possible CTD were taken from 51 mothers, yielding five that were positive. Twenty-one of these mothers whose histories were negative for CTD had blood samples taken for laboratory studies including analysis of immunoglobulins, C3, C4, and antinuclear factor (ANF); five mothers who had produced seven babies with CHB had positive results. As controls, 24 mothers were studied who had delivered normal babies or babies with other cardiac abnormalities. None had any history or symptoms suggesting CTD, and none showed any serological abnormality; their mean serum IgG concentration was 11·4 g/l (range 9·0-14·5 g/l).

Table I summarises the details of our 27 cases. In cases 1-20 various forms of maternal CTD had been evident at delivery or had become so later (four mothers of five babies with CHB); in cases 21-27 the mothers had positive serological findings only. CHB had been diagnosed at or before birth in 24 cases. Five of the 27 infants had other cardiac abnormalities (one partial anomalous pulmonary venous drainage; one patent ductus; and three anatomically corrected transposition of the great arteries, associated with a ventricular septal defect in one case and an atrial defect in another); none of these babies died.

Table II gives the details of 40 cases documented by other workers. Most of the mothers were regarded as having frank clinical CTD, but seven had positive serological findings only. Of the total series of 55 mothers, 21 (38%) mothers of 27 babies with CHB had or developed an illness diagnosed as SLE, while 9 (16%) mothers of 10 babies with CHB had rheumatoid arthritis. Fourteen (25%) mothers of 16 babies with CHB had CTD of a rarer or less specific form, while 11 (20%) mothers of 14 babies with CHB had serological abnormalities only. In only seven of the 67 cases were the mothers known to be receiving steroids or related treatment.

Of all the 67 children, 25 were boys and 42 girls. Five of the babies had transient skin lesions suggestive of discoid LE, with biopsy

confirmation in two; in one case a sibling had shown such a lesion, while one baby also had transient thrombocytopenia. In 22 cases there were known siblings with CHB. With two exceptions (cases 14 and 43) CHB was complete. In case 14 the block was partial, and in case 43 it was intermittent at birth and sinus rhythm was established at 6 months; a histological diagnosis of discoid LE was obtained in this case, and an older sibling had CHB.

Fifteen (22%) babies died, nine in the neonatal period. Necropsy studies were documented in nine cases. In seven cases endomyocardial fibrosis was recorded; in two of these cases and one of the others subendocardial calcium deposits were detected. In three cases attempts were made to identify the conduction system histologically, but in none was a clearly defined atrioventricular node found.

Discussion

Pregnancy in women with SLE results in a perinatal wastage rate of about 30%.[5-7] So when the severe immunological disturbance in SLE was recognised and abnormal IgG serum components identified the possibility was considered that these might cross the placenta and affect the baby. Generally IgG molecules cross the placenta freely, while molecules of IgA and IgM do not, and it was confirmed that certain of these abnormal IgG factors were present in cord blood.[8 9] No disease manifestations were observed in the babies, however, so it was concluded that these IgGs did not transfer the maternal disease.

There are now conclusive reports that babies may show some signs of maternal SLE.[10] Most reports describe a classical "butterfly" facial rash, some with histological confirmation of the disease, while leucopenia and thrombocytopenia have also been recorded. The manifestations have usually disappeared within three months. This behaviour is similar to that seen in babies born to women with other immunological diseases, notably Graves's disease, idiopathic thrombocytopenic purpura, and myasthenia gravis. In these there is good evidence that the transient effect is produced by placental transfer of maternal IgG antibodies to antigens expressed in the baby. The duration of the effects is in keeping with the known degradation time of IgG. The reversibility is probably because in two of these conditions (Graves's disease and myasthenia gravis) the antibody effect is on function, whereas in idiopathic thrombocytopenic purpura the target tissue has a high rate of replacement. The transient dermatological and haematological effects occasionally seen in babies born to mothers with CTD may be attributed similarly to a transplacental factor,[10] and some babies with CHB and their siblings showed such effects. In CHB the effect is commonly permanent, but circumstantial evidence suggests that CHB associated with maternal CTD is also due to a transplacental factor. In CHB the tissue affected presumably lacks the ability to undergo repair readily.

SLE is now regarded in one of its facets as an immune-complex disease, and McCue *et al*[11] suggested that immune complexes cross the placenta and produce the CHB. We can find no evidence that immune complexes cross the placenta; if they are concerned, more probably they form in the baby's system in response to pathological IgG antibody from the mother.

TABLE I—*Details of 27 cases of CHB recorded in present series*

Case No	Sex	Details of siblings	Course of child's illness	Maternal details
1	F	0	Symptom-free at 11 years	Symptoms from seven years before pregnancy; corticosteroids early in pregnancy; SLE diagnosed two years later
2	F	0	Symptom-free at 6 years	SLE diagnosed nine years before pregnancy
3	M	?	Died at 9 days	CTD for 10 years before pregnancy; three abortions; icterus during pregnancy
4	F	3, healthy	Symptom-free at 13 years	SLE from before pregnancy; prednisolone 10 mg daily during pregnancy
5	M	0	Symptom-free at 1 year	Sjögren's syndrome/SLE from six years before pregnancy; prednisolone 5 mg daily during pregnancy
6	F	1 younger, now healthy; neonatal neutropenia	Died at 1 day	Rheumatic pericarditis eight years before pregnancy; SLE diagnosed shortly after
7	F	?	Symptom-free at 8 years	Progressive SLE developed after pregnancy
8	M	2 older: 1 healthy, 1 died at 1 day	Rash at birth ("erythema multiforme") disappeared by 1 week; symptom-free at 10 years	CTD from before pregnancy
9	F	2 older: 1 with pacemaker for conduction defect, 1 died from leukaemia	Symptom-free at 40 years	Died 11 years after pregnancy from multisystem CTD
10	M	0	Symptom-free at 7 years	Symptoms from seven years before pregnancy; perimyocarditis in pregnancy; SLE diagnosed; corticosteroids in last trimester; died of renal failure five years after pregnancy
11	M	2 older: 1 healthy, 1 stillborn	Symptom-free at 14 years	CTD with features of RA developed five years after pregnancy
12	F	1 older, healthy	Symptom-free from heart block; developed SLE at 15 years	Arthritis for "many years"; hypothyroid; ANF 1:400 found when child's SLE diagnosed
13	F	0	Symptom-free at 29 years	RA for "many years"; multisystem CTD confirmed nine years after pregnancy; hypothyroid
14	M	1 older, healthy	Partial block (atrioventricular type 2); pacemaker inserted because of failure at 5 months; symptom-free at 2 years	RA from before pregnancy; ANF 1:100, speckled
15	M	1 with CHB (case 16)	Symptom-free at 15 years	RA from five years before pregnancy; ANF 1:100, homogeneous
16	F	1 with CHB (case 15)	Symptom-free at 12 years	
17	F	1 older, healthy	Symptom-free at 30 years	RA with deformities for "many years"; never treated in hospital
18	F	1 younger, healthy	Symptom-free at 19 years	RA from 12 years before pregnancy; never treated in hospital
19	M	1 younger, healthy	Had partial anomalous pulmonary venous drainage; operated on at 21 years, then pacemaker inserted	RA from two years before pregnancy
20	F	1 older, healthy	Symptom-free at 21 years	RA developed 16 years after pregnancy
21	M	0	Born at 31 weeks, died at 2 days	No symptoms. IgG 25·1 g/l (normal 12·8 ± SD 4·6 g/l); ANF 1:10, homogeneous; mother had SLE
22	F	1 older, healthy	Stokes-Adams attacks at 2 years; pacemaker inserted; symptom-free at 6 years	No symptoms. IgG 21·0 g/l; ANF 1:25, homogeneous
23	M	2 younger, healthy	Symptom-free at 8 years	Vague joint symptoms only; ESR 44 mm in 1st hour; IgG 20·05 g/l; C4 30%
24	F	1 older, healthy	Pacemaker inserted at 3 months because ventricular rate 30; symptom-free at 3 years	No symptoms. IgG 21·0 g/l
25	F	2 younger, both with CHB (cases 26, 27)	Symptom-free at 12 years	No symptoms. IgG 21·0 g/l; C4 40%
26	F	1 older, 1 younger, both with CHB (cases 25, 27)	Died at 6 months from Stokes-Adams attacks	
27	F	2 older, both with CHB (cases 25, 26)	Pacemaker inserted for suspected sinoatrial attack at 3 years; increasing failure at 8 years	

RA = Rheumatoid arthritis.

TABLE II—*Details of 40 cases of CHB taken from other reports*

Reference	Case Nos	Sex	Sibling/abortion data	Remarks
Hogg (1957)[24]	28	M	?	SLE diagnosed two years before pregnancy; steroid treatment throughout pregnancy
Wright *et al* (1959)[25]; Plant and Steven (1945)[26]	29, 30, 31	F, F, M	All 3 sibs affected	Mother died of SLE six years after birth of youngest sib
Hull *et al* (1966)[27]	32	M	Sib 4 affected; sibs 1 and 2 healthy; sib 3, transient cutaneous LE	Mother developed SLE before second pregnancy
Leduc *et al* (1968)[28]	33, 34	M, F	Sibs	Maternal SLE
Romano *et al* (1975)[29]	35	F	?	Maternal SLE
Chameides *et al* (1977)[30]	36, 37	F, F	Sibs	Maternal SLE from 18 years; pericarditis in second pregnancy; died four years later
	38	F	?	Maternal cutaneous LE for 10 years; SLE diagnosed shortly after delivery; died four years later
	39	M	?	Maternal SLE diagnosed 10 years before pregnancy
	40	F	?	Arthritis/nephritis one year after delivery; lupus nephritis (biopsy) three years later; "hypocomplementaemia with cutaneous vasculitis and arthritis"
	41	F	?	Maternal SLE 15 months after delivery; died two years later
	42, 43	M, F	Only sibs; 2 abortions	Maternal SLE from before birth of case 42; case 43 had hepatosplenomegaly with neonatal discoid LE (confirmed by biopsy); intermittent block only; sinus rhythm at 6 months; rash faded; grandmother of siblings had SLE
McCue *et al* (1977)[11]	44	M	One sib unaffected; 2 abortions	CTD from before pregnancy
	45, 46	F, M	Sibs; 1 other unaffected; 1 abortion	CTD developed at 1 year in case 45
	47	M	2 healthy sibs	CTD from before pregnancy
	48	F	Healthy sib	CTD from two years after pregnancy, then LE encephalitis
	49	F	2 healthy sibs	CTD from before pregnancy
	50	M	2 healthy sibs	CTD from before pregnancy
Winkler *et al* (1977)[31]	51, 52	F, F	Only sibs	Case 51 had thrombocytopenia and transient rash, histologically LE; maternal CTD from before pregnancy but SLE confirmed only when congenital LE diagnosed in baby
Berube *et al* (1978)[32]	53	F	?	CTD before pregnancy; baby developed transient discoid LE
	54	M	0	CTD before pregnancy; took prednisolone 10 mg daily throughout pregnancy
	55	F	0	ANF + + + 1:80; latex +; "sensitised human cell titre" 1:40
McCue *et al* (1977)[11]	56	F	2 healthy sibs	C4 54%; latex +; "sensitised human cell titre" 1:80
	57, 58	F, F	Twins, both affected; 2 other sibs healthy	Latex +; "sensitised human cell titre" 1:80
	59	M	1 healthy sib	ANF + + 1:20
Altenburger *et al* (1977)[33]	60	M	?	ANF 1:16-1:64
Aylward (1928)[34]	61, 62	F, F	2 intervening male sibs healthy	Maternal Mikulicz's disease (Sjögren's syndrome)
Syed (1978)[35]	63	M	1 older sib, healthy	Maternal RA diagnosed after first pregnancy
Hardy *et al* (1979)[36]	64	F	1 induced abortion; 1 healthy sib	Maternal SLE for eight years before pregnancy; baby had transient skin lesions
	65	M	1 induced abortion	Maternal SLE and Sjögren's syndrome for four years
	66	F	?	Maternal joint pain, anaemia, rashes, ANF +
	67	F	1 healthy sib	ANF 1:10; rheumatoid factor 1:64

Another explanation is a "slow" virus, but if this were the case we should expect the disease often to be be progressive after birth. In only one case did a child go on to develop SLE (at 15 years), while another developed rheumatoid arthritis at 4½ years. These exceptions may reflect an inherited genetic predisposition to CTD unrelated to the effect evident on the heart at birth.

In the AEPC study, covering 583 cases, there were only 15 families with multiple siblings affected,[12] yet of the 67 children reviewed here, 22 had known affected siblings. This suggests that in the cases of CHB related to CTD an influence transmitted from the mother was relatively important. We did, however, trace one mother of three children with CHB, two of whom died, who had neither symptomatic nor serological evidence of CTD. The association between CHB and maternal CTD is most evident when consideration is started from the less common condition, CHB. We calculate that about one in three mothers who deliver babies with CHB have or will develop symptoms or signs of CTD. McCue *et al*[11] concluded that the proportion may exceed 60%. The difference is small when considered against a chance association of one in many million. The incidence of serious maternal CTD may indeed be higher than our review suggests, since in the AEPC group several mothers died at an early age from renal insufficiency.

Most of the recently reported cases and those in our series were from paediatric cardiological clinics dealing mainly with babies who survive the immediate neonatal phase. The baby with CHB may be born in a critical state and fail to establish an extrauterine existence; others probably die in utero undiagnosed. Such cases will rarely be recorded. The 22% mortality rate is therefore probably an underestimate. Lev *et al*,[13] reporting on seven necropsies on infants with CHB, found fibrosis and in some cases calcification in the most distal part of the atrial musculature. All cases showed relatively advanced fibroelastosis. Hence death is probably related to the extent of myocardial fibrotic damage.

There is evidence that chronic heart block in adults may have an immunological basis.[14 15] It rarely occurs in adults with SLE,[16] and the question arises why the baby tends to be susceptible. Possibilities include an effect on phase-specific cardiac antigens, present in fetal and neonatal life but absent later. Alternatively, "blocking" antibodies in the maternal system may protect the myocardium from the noxious antibodies but be unable to cross the placenta and therefore fail to protect the baby's heart. It may be relevant that two mothers (cases 10 and 37) had perimyocarditis and pericarditis during pregnancies resulting in affected babies; one of the mothers also had an earlier affected child.

In view of the 9:1 female preponderance of SLE[17] it is interesting that the preponderance of girl babies with CHB was less than 2:1. This suggests that the sex factor operates at the level of SLE initiation rather than at receptor level in the tissue ultimately damaged.

That some mothers did not have signs of their CTD at the time of birth of the affected baby accords with findings in other immunological diseases affecting the baby[10] and with knowledge that macrosomatic babies may be born years before a mother has clinical or biochemical evidence of diabetes.[18] Just as birth of an overweight baby is regarded as a portent of diabetes in later life, so birth of a child with CHB to a healthy mother should arouse suspicion that she will ultimately develop CTD.

Bresnihan *et al*[19] noted that in pregnancies complicated by SLE and ending in abortion there was a higher incidence of antitrophoblast antibody than in mothers with SLE whose pregnancies went to term. Grennan *et al*[20] found deposition of immune complement in the trophoblast of mothers with SLE similar to that described on glomeruli. Both these observations point to immunological factors influencing reproductive wastage in SLE. The association between CHB and CTD also does so and opens avenues for further study. Definition of the relevant antibody and antigen should further elucidate the pathogenesis of the two conditions and help towards understanding the very high and unexplained perinatal loss in SLE. It should then be possible to predict when a woman is likely to produce an infant with CHB and give family planning advice or arrange special neonatal care and so reduce the incidence and mortality. It may

even be that specific antenatal treatment will protect the baby from harmful antibody, as has been done with high thyroid-stimulating antibody concentrations in Graves's disease corrected surgically.[21-23]

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Mortality in patients with haematemesis and melaena: a prospective study

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Summary and conclusions

In a prospective study of death in 817 patients with haematemesis and melaena admitted on 894 occasions, the protocol included admission of all patients to a defined unit, early endoscopy and resuscitation, and planned management. Over the three consecutive two-year periods of the study mortality significantly decreased from 9% to 2·4%. Although the operative rate remained the same, the operative mortality fell from 16% to 1·6%. The fall in mortality was greatest in patients with bleeding gastric ulcers.

These results suggest that prospective studies with a defined policy can influence the mortality in patients with upper gastrointestinal bleeding.

Introduction

In a retrospective study Schiller *et al*[1] found that mortality in patients with upper gastrointestinal bleeding had remained constant. A pilot study at this hospital in 1971 indicated a mortality of 15% in such patients. Prospective studies seem to have advantages over retrospective series because management may be simplified, complete data may be collected, and an agreed policy produces consistency in management. In October 1972 a unit with a defined management policy was established to which all patients presenting to the hospital with upper gastrointestinal bleeding were admitted. We report here the mortality from upper gastrointestinal bleeding during the past six years.

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Patients and methods

During the six years of the study 817 patients were admitted on 894 occasions, giving a monthly admission rate of 12·4. Management policy was based on close liaison between the gastroenterologist, surgeon, and gastroenterology registrar, and defined indications were established for surgery. Patients underwent endoscopy with the forward-viewing Olympus or ACMI instrument within 12 hours after admission. In all patients an intravenous line was inserted; in those who were shocked or bleeding massively a central venous catheter was inserted. The indication for blood transfusion was shock or a haemoglobin concentration of less than 10 g/dl. Admission was to a separate area in a general surgical ward but subsequently all patients with oesophageal varices requiring a Sengstaken-Blakemore tube were nursed in the intensive care unit, as were all patients postoperatively.

Surgery was indicated in patients with chronic duodenal or gastric ulcer surgery by recurrent bleeding, and in patients over 50 who were shocked on admission or required over 5 units of blood. In the past two years cimetidine has replaced intragastric instillation of milk and aluminium hydroxide gel as the basic treatment for acute peptic ulcer or erosive gastritis. Continued or massive bleeding from acute peptic ulceration with a transfusion limit of 10 units was the indication for surgery in such cases. With bleeding oesophageal varices the basic