CONGENITAL SYPHILITIC NEPHROSIS

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Abstract. Analysis of congenital syphilis in 455 infants and neonates between 1977 - 1991 in Children's Hospital, Bangkok, Thailand revealed 11 cases (2.4%) with evidence of congenital syphilitic nephrotic syndrome which were confirmed by clinical, serologic and laboratory findings, long bone x-rays and renal biopsy. Ages of all 11 cases were between 1 day to 2 months (mean 24 days); 6 were boys and 5 girls. Two of them died because of necrotizing enterocolitis and sepsis respectively; the mortality rate was 18%. The other nine had complete recovery following penicillin therapy.

INTRODUCTION

The development of the nephrotic syndrome in early infancy brings to mind a limited number of etiologic diagnoses. Among the diseases to be considered are congenital nephrosis (microcystic disease), idiopathic nephrotic syndrome of childhood (minimal lesion syndrome), intrauterine infections such as rubella, toxoplasmosis, cytomegalovirus, and congenital syphilis. The increasing incidence of syphilis in neonates should result in more cases of nephrotic syndrome, although this is a rare complication in syphilitic infection (Hill *et al,* 1972).

Renal disease in early infancy due to congenital syphilis was first reported in 1871 by Brandley (Papaioannou *et al,* 1961), who described "syphilitic renal dropsy" in an infant. Since then scattered reports of congenital syphilis presenting as the nephrotic syndrome or nephritis in the newborn infant and in early infancy have appeared. Recent investigations of renal disease, however, have not placed much emphasis on congenital syphilis as the etiology of the nephrotic syndrome in early infancy (Papaioannou *et al,* 1961).

In the past direct injury during the spirochetemic phase, antisyphilitic therapy with heavy metals and penicillin, increased susceptibility to poststreptococcal glomerulonephritis, and antigen-antibody reactions have been suggested as possible pathogenic mechanisms, but now it is well accepted that this disease is an immune complex mediated glomerulopathy (Wiggelinkhuizen *et al,* 1973).

Congenital syphilis as a cause of nephritis or the nephrotic syndrome is exceedingly rarely encountered in the literature, although accurate statistics are not available as to its incidence. Lereboullet and Lelong (cited by Scully and Yamazaki, 1949) in a survey of the literature to 1930 were able to cite only 15 cases, in which renal findings were prominent in syphilitic infants. In 1942, Wile and Mundt (cited by Pollner, 1966) reviewed 500 cases of congenital syphilitic infants and adults : none had renal disease.

Platou and his associates (cited by Scully and Yamazaki, 1949) reviewed 122 cases of congenital syphilis treated with penicillin; no definite cases of nephropathy were seen.

The renal lesion has been considered to result from the invasion of the kidney by spirochetes or to be secondary to hypersensitivity reaction. Immune complex deposition has been implicated in the pathogenesis of the nephrotic syndrome associated with syphilis. On light microscopy, slight to moderate thickening of the basement membrane has been found to be the major lesion. The epithelial and endothelial cells are prominent. Immunofluorescent IgG staining is seen in a nodular pattern along the capillary basement membrane, and fibrin is present in the same distribution. The demonstration of *Treponema pallidum* antigen is negative (Kaplan *et al,* 1972).

Thomas and Schur (cited by Scully and Yamazaki, 1949) accepted the division of syphilitic nephropathies into syphilitic nephritis and syphilitic nephrosis. They pointed out that urinary findings may vary from mild albuminuria with a few unusual elements in the sediment to extensive albuminuria associated with a few or a large

number of casts. Red blood cells may be absent during the entire period of observation, or they may vary in numbers from an occasional cell to almost gross hematuria.

The usual picture of early syphilitic nephrosis as described by Thomas and Schur (cited by Scully and Yamazaki, 1949) is characterized by heavy albuminuria, casts with few or no red blood cells and low cylinduria. Renal function is rarely impaired, BUN remains normal. Thomas and Schur used the degree of albuminuria and hematuria as the chief criteria in separating nephritis from nephrosis.

Scully and Yamazaki (1949) criteria for diagnosis of congenital syphilitic nephropathy in an infant are :

1. Unequivocal concomitant evidence of congenital syphilis and/or consistently positive reaction in serologic tests for syphilis beyond the age of 12 weeks (roentgenographically demonstrable infectious osteochondritis and/or periostitis is desirable).

2. Evidence of syphilitic disease in the mother.

3. Unmistakable evidence of nephrosis or nephritis, with causes other than syphilis absent.

4. Prompt disappearance of renal abonormalities on the administration of adequate antisyphilitic thrapy and their nonrecurrence.

CASE DATA AND DISCUSSION

The data for 11 cases fulfilling these criteria are presented in Table 1 - 6.

All 11 infants presented were syphilitic as evident by positive VDRL reactions with titers ranging from 1:8 to 1:128 with a geometric mean titer (GMT) of 21.9. Five patients (cases 2, 3, 4, 8 and 10) were additionally tested by FTA-ABS and all were positive. All of their mothers were VDRL positive on admission with titers ranging from 1:8 to 1:128 (GMT 21.9), whereas only 2 paternal sera (cases 2 and 4) were positive each with a titer of 1:32. Four of 11 mothers (cases 1, 2, 10 and 11) attended the antenatal clinic, of whom 3 (cases 1, 2 and 10 were VDRL positive. Two VDRL positive mothers did not receive treatment, but one (case 10) received a single dose of benzathine penicillin at three months into pregnancy.

All 11 patients had all the accepted characteristic manifestations of the nephrotic syndrome : edema, proteinuria, hypoproteinemia, hypoalbu-

Table 1

Age and Sex

Case	Sex	Age at onset (day)	Body weight in		Delivery
			at birth	at onset	
1	M	9	-	2,700	Normal
2	F	57	2,470	3,700	Normal
3	F	50	3,200	4,400	Normal
4	F	13	2,100	1,700	Abnomal, term AGA
5	M	30	2,500	2,600	
6	M	1	2,300	2,300	Abnormal, SGA with placenta insufficiency gr 3.
7	M	1	2,100	2,100	Abnormal, 32 wks AGA
8	M	41	2,200	3,400	
9	F	60	3,750	3,300	
10	F	1	3,400	3,400	Abnormal, hydrops fetalis apgar scores 1 - 3
11	M	1	1,750	1,750	Abnormal, 36 wks SGA caesarean section apgar scores 4 - 6

minemia and hyperlipidemia. Only 3 patients (cases 9, 10 and 11) had serum cholesterol levels below 250 mg/dl (214, 182 and 172 mg/dl, respectively) (Table 4). However, Pollner (1966) reported that normal infants have low cholesterol levels ranging from 80 to 125 mg/dl. The observed elevations in the cases presented, which exceeded this level, can thus be as important as the striking elevations seen in older children. It is known that the serum cholesterol level is lower when the nephrotic syndrome occurs during infancy.

Other causes of nephrotic syndrome in infants comprising rubella, toxoplasmosis and cytomegalovirus (CMV) infection had been ruled out by relevant serological tests (hemagglutination inhibition and IgM ELISA for rubella, hemagglutination for toxoplasmosis and IgM ELISA for CMV infection). We propose that in all cases of nephrotic syndrome in small infants where blood examination for rubella, toxoplasmosis, VDRL and urine examination for CMV are negative, renal biopsy should be done to differentiate congenital nephrotic syndrome (Finnish type) from idiopathic infantile nephrosis; the former should have microcystic dilatation of proximal convoluted tubules.

Radiologic changes of long bones (tibia, femoral), the features of syphilis, were seen in these patients of which the presence of radiolucent band was most common (cases 1, 4, 5, 8, 9, 10 and 11) followed in decreasing frequencies by periosteal new bone formation (cases 2, 3, 5, 7 and 8), irregularity of metaphyseal end of long bones (cases 4, 5, 6 and 11) and osteolytic lesion (case 8). Renal biopsy was performed in cases 1 and 2 : direct immunofluorescent staining showed granular deposition of IgG, IgM, fibrinogen and complement at the glomerular basement membrane similar to cases reported by Hill *et al* (1972) and Kaplan *et al* (1972).

Seven of 11 cases showed elevation of liver enzymes and bilirubin (Table 4) but none had im-

Table 2

Chief complaints and positive clinical findings

Case	Chief complaints	Hematocrit volume%	Jaundice	Edema	Erythematous rash	Liver (cm)	Spleen (cm)
1	irritable cried: could not stretch both legs (pseudoparalysis)	24	no	developed on 5th day of admission	+	2	2
2	chronic diarrhea	21	no	developed on 3rd day of admission	no	2	1
3	diarrhea 7 days edema 2 days convulsion	32	no	+	no	2	1
4	premature with sepsis	41	1 +	Dehydrated 2° to sepsis	no	2	1
5	edema for 3 days	27	+	+	+	2	1
6	RDS	35	+	+	no	3	2
7	RDS	26	+	+	no	2	1
8	fever 5 days dyspnea 2 days	27	+	+	no	5	2
9	fever 1 month	21	no	no	no	2	1
10	hydrops fetalis with cyanosis	27	no	edema with ascities	+	3	1
11	RDS	36	no	edema with ascities	skin cracked and peeling	5	2

paired renal functions. Twenty-four hour urine protein excretion was greater than 40 mg/kg body weight/day (nephrotic range) in all cases (Table 3).

Treatment given was penicillin 50,000 - 100,000 units/kg/day, usually for 14 days, but in cases in whom neurosyphilis was suspected (cases 2, 6) we gave penicillin for 21 days (Table 6). No patients received steroids.

Infants with congenital syphilitic nephrosis are susceptible to infections in the same way as general nephrotic patients and such increased susceptibility could be attributable to several factors comprising 1) decreased serum immunoglobulin, especially IgG; 2) urinary loss of transferrin which is important for iron transport and immunoregulatory function; 3) alteration of lymphocyte function and 4) occurrence of factors which inhibit neutrophil chemotaxis.

Table 3

Urinalysis data

Case	Urinalysis								
	Proteinuria			RBC	WBC	Casts			Bile
		mg/day	mg/kg			EPI	Granular	Hyaline	
1	3 +			neg	neg	-	1 - 2	-	-
2	3 +	490	132.43	-	1 - 2	0 - 1	-	-	-
3	3 +	3.8	863.06	18 - 20	8 - 20	1 - 2	-	-	-
4	4 +	175	102.94	10 - 12	1 - 2	1 - 2	-	-	-
5	4 +	205	78.84	30	1 - 2	2 - 3	-	-	4 +
6	2 +	-	-	1 - 2	2 - 3	0 - 1	-	-	2 +
7	3 +	-	-	18 - 20	2 - 3	1 - 2	-	-	-
8	3 +	-	-	1 - 2	4 - 6	-	-	-	-
9	3 +	245.9	74.5	8 - 10	4 - 6	-	1 - 2	-	-
10	2 +	124.8	37.59	3 - 5	3 - 5	-	-	-	-
11	3 +	74.2	43.64	2 - 3	5 - 7	1 - 2	10 - 12	3 - 5	-

Table 4

Blood chemistry

Case	Total protein g/dl	Alb g/dl	Glob g/dl	Cholesterol mg/dl	Bilirubin	Direct	Ind	SGOT	SGPT
1	5.0	2.7	2.3	280	-	-	-	-	-
2	4.2	1.21	2.99	215	-	-	-	-	-
3	6.7	1.9	4.8	342	-	-	-	-	-
4	6.95	2.92	4.03	356	7.1	4.6	2.5	310	140
5	5.1	1.55	3.55	260	9.0	4.6	4.4	400	250
6	5.1	1.7	3.4	255	29.5	13.0	16.5	290	50
7	3.96	1.97	1.99	270	7.7	3.5	4.2	154	73
8	5.19	1.57	3.62	242	3.72	2.81	0.91	120	60
9	5.0	1.95	3.05	214	-	-	-	-	-
10	3.29	1.81	1.48	182	17.6	2.75	14.85	240	49
11	6.63	2.97	3.66	165	13.9	1.35	6.55	360	280

Table 5

Results of lumbar puncture

Case	Lumbar puncture				
	Pandy	Cells	Protein mg/dl	Sugar mg/dl	VDRL
1	neg	no cell	-	-	nonreactive
2	neg	no cell	-	-	weakly reactive
3	neg	no cell	78	46	nonreactive
4	neg	mono 7	511	27	nonreactive
5	neg	mono 8	55	36	nonreactive
6	1^+	PMN 4 L 44	187	35	reactive 1:64
7	neg	no cell	95	38	nonreactive
8	neg	mono 5	39	62	nonreactive
9	neg	2 L	32.8	4:7	nonreactive
10		traumatic TAP			
11	1^+	no cell	17.7	27	nonreactive

Table 6

Treatment and complications

Case	Treatment	Complications
1	Procaine penicillin 30,000 units/day IM for 10 day, no response; second course of penicillin 150,000 units/day was given for 2 weeks with 4 plasma transfusions.	bronchopneumonia in both lungs
2	Penicillin G sodium 50,000 units per kg per day IM for 3 weeks	neurosyphilis; chronic diarrhea
3	Penicillin 400,000 units IM for for 2 weeks	no
4	Penicillin 100,000 units/kg/day IM for 14 days	prematurity sepsis hepatitis
5	Penicillin 150,000 units/day	necrotizing enterocolitis (NEC)
6	Penicillin 100,000 units/kg per day with gentamicin for 3 weeks	neurosyphilis RDS pneumonia RLL and LUL septicemia (*Pseudomonas* species) hepatitis
7	Penicillin 100,000 units/kg/day for 2 weeks, gentamicin 5 mg/kg/day for 10 days	preterm transient tachypnea of the newborn hepatitis
8	Penicillin 200,000 units/kg/day for 3 weeks	pneumonia both lungs
9	Penicillin 100,000 unts/kg/day for 2 weeks	gastroenteritis
10	Supportive treatment, packed red cell transfusion, exchange transfusion, combination of antibiotic IV (claforan, penicillin gentamicin)	hydrops fetalis hypoglycemia hyperbilirubinemia sepsis
11	Penicillin G sodium 200,000 units/kg/day IV for 2 weeks	pneumonia

The treatment outcome was favorable in all but 2 (cases 5, 10), who died of complications due to necrotising enterocolitis on day 21 and bacterial sepsis on day 44, respectively. The mean period of hospitalization (± SD) was 36 ± 21 days.

Congenital syphilis (Grossman, 1991) results from the transplacental infection of the developing fetus. An infected pregnant woman has a high probability of transmitting the infection to the fetus (90% probability during the secondary stage). *Treponema* organisms can cross the placenta at any stage of pregnancy but appear to elicit little tissue response before the 15th week of gestation. Adequate treatment of the mother with penicillin protects the fetus, but the mother may become reinfected. Fetal mortality is high in this infection, 25% of infected infants die *in utero* and perinatal death occurs in another 25% of infected babies. The signs and symptoms are varied and may appear at any time between birth and 3 months of life, 5 weeks being the median time of onset with many infants appearing perfectly normal at birth.

The disease can be prevented, serologic tests for syphilis should be performed in pregnant women, since the disease of infants can be prevented by treating the mother. Penicillin is the only drug that, when given during pregnancy, reliably protects the fetus. If other drugs such as erythromycin are used, the infant should be treated again after birth.

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