

# Hematological Aspects of Congenital Syphilis

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## ABSTRACT

Hematologic investigations for 7 years at the Pediatric Department of Yonsei Medical Center of 52 syphilitic infants were reviewed. A moderate degree of anemia with red cell regeneration was observed in 40 infants (76.0 %). Marked thrombocytopenia but without active bleeding was found in 19 infants, and with active bleeding in 3 infants. A wide range of leukocyte counts, relative lymphocytosis and monocytosis were prominent features. The jaundice was mainly due to unconjugated bilirubin in 6 infants, conjugated as well as unconjugated bilirubin in 8 infants. With therapy, the above abnormal hematologic findings showed marked improvement. Early diagnosis is essential. Prevention and congenital syphilis depend on a high level of clinical suspicion, supported by routine and diagnostic use of laboratory and serologic aids, in the asymptomatic or minimally symptomatic infants.

## INTRODUCTION

The association of hematologic abnormalities with congenital syphilis has been recognized for many years. These abnormalities are manifest early in the course of this disease, and apart from other physical and laboratory

findings, hematologic changes should point to the diagnosis of congenital syphilis. The study of hematologic abnormalities of this disease has received relatively little attention and has not been well documented in the past.

## CASE MATERIAL AND METHOD

During the past seven years from Nov. 1970 to Nov. 1976, congenital syphilis was diagnosed in 52 infants at the Pediatric Department of Yonsei University College of Medicine, with the serologic study among 7,469 infants (0.69%). The criteria of the diagnosis of congenital syphilis were clinical features consistent with syphilis and positive serology in either the mother or the child. Venereal Disease Research Laboratory (VDRL) tests were done on all 52 infants and mothers, with Reiter Protein Complement Fixation (RPCF), Kolmer titration and Fluorescent treponemal Antibody-absorbed (FTA-ABS) as supportive tests. All the infants were reviewed mainly by hematologic features and clinical findings. Infants born to seropositive mothers but with no hematologic reports were not included.

## RESULTS

The infants ranged in age from one to 123 days. The sex ratio was 1.4:1 with male predominance. There were nine premature and 43

X-ray changes (bone)	39(75.0)
Hepatosplenomegaly	38(73.1)
Skin and mucocutaneous manifestation	30(57.7)
Snuffles	22(42.3)
CNS involvement	13(25.0)
Jaundice	9(17.3)
Edema	4(7.7)
Pseudoparalysis	1(1.9)
None	3(5.8)
Symptom	Number of patients(%)

Fig. 1. Clinical and laboratory findings in 52 syphilitic infants

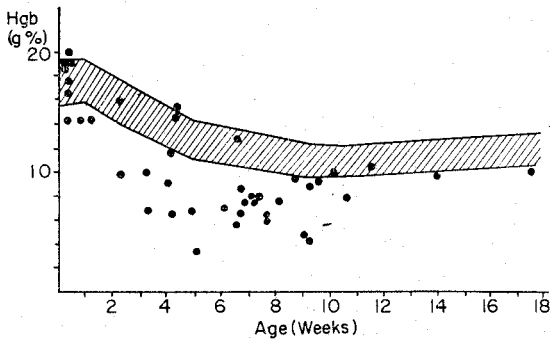


Fig. 2-A. Hemoglobin level at diagnosis in full term infants (normal hemoglobin were from Matoth et al)

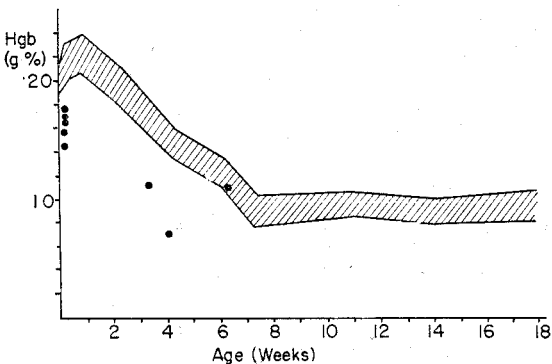


Fig. 2-B. Hemoglobin level at diagnosis in premature infants (normal hemoglobin were from Schulman)

full-term infants and three died. An autopsy was done in one infant with florid evidence of syphilis. Severe respiratory distress, anemia

even after transfusion and massive kidney damage may be the causes of the death. Over half of infants were initially diagnosed to have some other disease such as sepsis, congenital nephrosis, blood group incompatibility, cytomegalovirus or toxoplasmosis infectibility, cytomegalovirus or toxoplasmosis infection and congenital heart disease. The exact diagnosis was made after results of the serologic tests of the infants and mothers or typical findings of roentgenograms of the bone.

Figure 1 indicates the frequency of positive clinical and laboratory evidence in these 52 infants. X-ray on bone, hepatosplenomegaly and skin and mucocutaneous manifestations were positive in over half of the infants, and jaundice, edema, pseudoparalysis were infrequently present on admission. Three of them showed no positive findings on admission. Three of them showed no positive findings on admission, but VDRL tests of their mothers were positive and they had histories of premature delivery.

### HEMATOLOGIC DATA

Anemia: The results of the hematological investigations are shown in Table 1. Some degree of anemia was noted in 40 infants

Table 1. Initial Hemogram of 52 Syphilitic Infants

Case No.	Age (days)	Hgb. (Gm%)	Hct. (%)	Retic (%)	Platelet ( $\times 10^3$ )	WBC ( $\times 10^3$ )	Differential count (%)					Nucleated erythrocyte	
							Neutrophils			Lym.	Mono.		eos baso
							Juv.	Stab.	Seg.				
1	1	19.3	60	6.0	adequate	20.2			76	24			
2	1	18.6	58		adequate	16.0	1	5	25	54	14	1	
3*	1	17.3	51	10.5	adequate	13.5				63	37		1
4*	1	15.8	50		adequate	22.0		21	29	44	6		
5*	1	17.1	52	15.1	1.0	24.8	2	10	51	26	10	1	37
6	1	16.4	47	5.5	adequate	11.4			35	62	1	2	
7*	1	16.2	50	8.0	8.4	39.5			47	38	12	3	
8*	1	14.9	43	6.5	6.4	8.8			38	57	5		4
9	2	19.3	53		adequate	24.3	3	7	51	38	1		
10	3	20.0	64	5.1		20.4		1	47	39	12	1	
11	3	17.5	55		3.2	15.8	10	23	22	43	2		
12	3	16.6	50		12.6	28.6			35	58	7		
13	3	14.4	44	7.8	adequate	29.5			18	77	5		7
14	7	14.3	43	2.4	adequate	18.7			45	8	2		
15	9	14.5	45	6.0	12.0	34.5		9	44	37	9	1	1
16	16	16.1	49		7.7	11.7		4	29	58	7	2	
17	16	9.9	30		9.6	5.0	5	6	28	56	4	1	
18	20	9.9	32	8.1	adequate	22.4		2	55	39	4		
19*	23	11.6	34	6.5	7.7	35.5		8	52	21	19		
20	23	10.2	33		adequate	29.3		5	48	39	8	4	
21	23	6.7	18	9.8	2.4	16.2			34	61	5		
22	26	9.2	28	4.8	3.4	24.5		9	42	44	3	2	2
23*	27	7.2	25	8.0	1.6	15.4			33	62	5		4
24	28	12.2	35	4.2]	5.6	28.5		2	40	51	7		
25	28	6.3	20	12.0	1.8	7.0	3	4	10	81	2		14
26	29	15.2	49		adequate	19.0			29	58	13		
27	30	16.0	48		adequate	13.3		4	62	27	5	2	
28	33	6.5	23		adequate	16.2		24	25	48	2	1	
29	36	3.5	10	5.1	2.0	70.0	3	1	47	42	6	1	3
30	41	6.6	23	9.0	4.6	13.7	14	2	40	41	1	2	6
31*	42	11.5	36	10.3	adequate	9.7	4	38	50	8			
32	45	13.0	38	4.1	adequate	22.3		1	36	59	3	1	
33	45	5.6	18	8.9	adequate	11.7	5	5	21	65	4		
34	45	9.0	27	2.1	6.4	21.1			25	57	3	15	8
35	45	6.7	22	1.0	11.4	18.6	3	3	29	55	8	4	
36	47	8.3	27	9.5	adequate	21.8			25	73	2		
37	48	8.1	24	6.5	adequate	10.8		5	39	48	7		
38	49	7.8	24	5.8	11.0	26.2	6	5	40	44	3	2	6
39	50	8.7	24	8.8	4.8	21.9		29	36	25	10		

Case No.	Age (days)	Hgb. (Gm%)	Hct. (%)	Retic (%)	Platelet ( $\times 10^9$ )	WBC ( $\times 10^9$ )	Differential count (%)					eos. baso.	Nucleated erythrocyte
							Neutrophils			eos. baso.	Nucleated erythrocyte		
							Juv.	Stab.	Seg.				
40	52	6.6	16	11.0	adequate	8.8		2	22	70	3	3	3
41	52	6.9	24	10.4	3.6	36.5	1	5	24	63	7		3
42	55	8.5	29	7.7	11.4	13.9		2	33	63	2		
43	62	5.3	14	8.8	adequate	18.3		11	46	40	3	1	
44	65	10.2	33	8.8	8.2	20.6		5	55	34	6	4	
45	66	5.7	17		2.0	14.6		1	23	74	2		
46	67	10.4	31	3.5	8.6	15.0	1	4	72	19	4		1
47	70	11.0	38	5.0	adequate	24.0	1	3	39	48	7	2	
48	71	6.8	21	4.0	7.8	23.8		14	54	28	4		1
49	75	8.6	28	9.0	2.2	45.3	17	20	15	42	6		9
50	81	12.0	36		adequate	14.8			23	72	5		
51	99	11.0	35		adequate	19.8		4	17	75	3	1	
52	123	10.9	33		adequate	14.8		2	30	58	10		

\* Premature infant

(76.0%). Eight of nine premature infants and 29 of the full-term infants except one showed evidence of associated active red cell regeneration with reticulocytosis ranging from 2.1 to 15.1 percent (Table 1, Figure 3).

Two more infants developed anemia during admission. Peripheral smear showed normocytic, normochromic erythrocytes with increased polychromasia and many nucleated erythrocytes (one to 37 per 100 leukocytes) (Table 1), and there were also occasional burr cells and spherocytes.

Figures 2-A and 2-B show the distributions of hemoglobin levels in 43 full-term and nine premature infants. Some degree of anemia was noticed in 32 full-term infants, and two of them showed no decreased hemoglobin level at first, but showed pronounced decrease with serial determinations. In those infants, even with high hemoglobin levels on the first admission day, reticulocytosis was prominent, which continued for a long time. Eight of the nine premature infants showed decreased

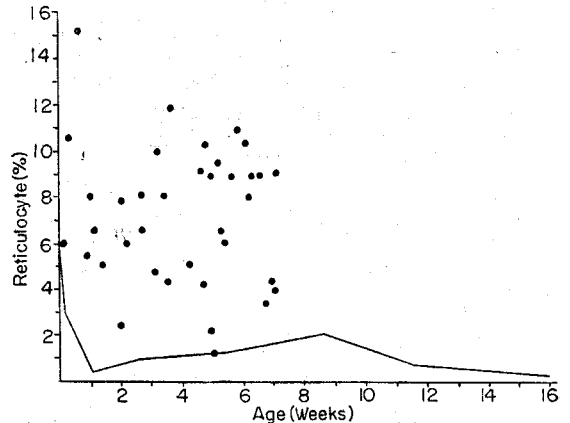


Fig. 3. Reticulocyte count at diagnosis (37 infants)

hemoglobin levels below normal range, and some degree of reticulocytosis was noticed (5.5 to 15.1%) (Figure 3).

A bone marrow aspiration in case number of 49 was done at the 27th day, which revealed normal cellularity with erythroid hyperplasia. Nonbudding megakaryocytes were increased in number. With this pattern, the anemia present in this syphilitic infant closely resembles that

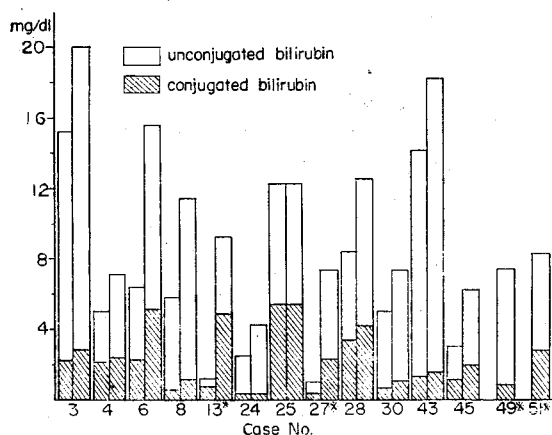


Fig. 4. Platelet count at diagnosis (27 infants)

seen in erythroblastosis fetalis due to blood group incompatibility. The anemia and hepatosplenomegaly showed definite correlation with the p-value below 0.01. Thirty of the 38 infants with splenomegaly showed gradual decrement in the spleen size during penicilline therapy. In an autopsied case, the spleen was 10 times as large as normal for his age.

**Thrombocytopenia:** Platelets were counted exactly in 27 infants and the others showed adequate platelets on the peripheral smears. Platelets ranged from  $14,000/\text{mm}^3$  to  $126,000/\text{mm}^3$  which were all below normal ranges ( $16,000$  to  $400,000/\text{mm}^3$ ). However significant decrease with the range below  $100,000/\text{mm}^3$  was present in 22 infants, and among them three were below  $20,000/\text{mm}^3$  (Figure 4). A bone marrow aspirations showed increased numbers of non-budding megakaryocytes even with a decreased number of platelets on the peripheral smear. Bleeding history and bleeding diathesis were present in five infants, and platelets were adequate in the peripheral smear and another three were below  $100,000/\text{mm}^3$ .

**Leukocytosis:** Leukocyte counts ranged from  $5,000$  to  $70,000/\text{mm}^3$  (mean of  $21,000/\text{mm}^3$ ) with wide variation in the differential count

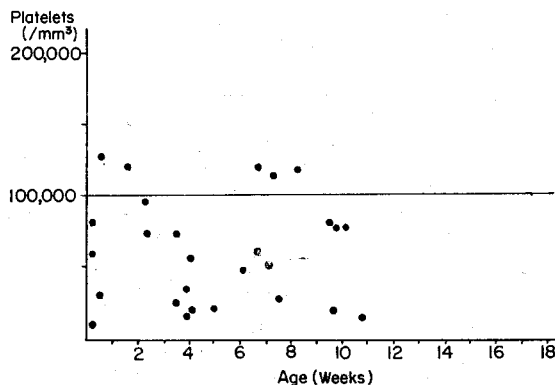


Fig. 5. Initial and peak serum bilirubin levels in each case. \* not jaundiced on admission

(Table 1). There was no correlation between leukocyte count and the severity of the infection, or between the differential count and the severity of the infection. However relative lymphocytosis were noticed, and with treatment, gradual decrease in the number of immature cells, and monocytes was remarkable. Statistical study was not done on the differential count.

**Jaundice:** Clinical jaundice was present only in 10 infants on admission and four other infants developed jaundice during hospitalization; one of them showed hyperbilirubinemia suddenly on the third day of life. Initial and peak serum bilirubin levels are shown in Figure 5. Serum glutamic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) levels were within normal range in two tested infants. At an autopsy of one case, the liver was five times too large for his age and microscopic findings showed extramedullary hematopoiesis in the sinusoids and many inflammatory cells around the blood vessels and bile ducts in the portal triad.

The jaundice was mostly due to unconjugated bilirubin in six infants among 14 jaundiced infants, and in the other eight infants, was

due to conjugated as well as unconjugated bilirubin.

## DISCUSSION

Syphilitic infants may have no clinical symptoms during the first few weeks or months of life (Vaughan and McKay 1975). But with our careful observations, there were many infants with certain degree of abnormal hematologic findings in the asymptomatic or early stages of congenital syphilis associated with serologic changes. And the purpose of this report is to provide the early diagnosis of congenital syphilis by supporting other laboratory findings in the asymptomatic or with minimal clinical symptomatic infants.

In anemia of the immediate neonatal period and the next six months, congenital syphilis must be bourn in mind. There has been a long recognition of the association of congenital syphilis and anemia, but its frequency is not well known (Barr *et al.*, 1963; Hochsingr, 1909; Jeans and Cooke, 1930; Leos, 1892; Nabarro, 1954; Piney, 1932; Platou and Kohara 1950; Sevestre, 1909; Zelensk and Cibulski, 1894; Stokes *et al.* 1944). We found a moderate degree of anemia in 40 of 52 infants (76.0%), which was somewhat less frequent than another report (Whitaker *et al.*, 1965). There is no definite known cause of anemia in congenital syphilis, but the anemia is explained by many possible causes such as hemolysis, interference with hematopoiesis, hypersplenism and nutritional deficiency (Barr *et al.*, 1963; Nabarro, 1954; Jeans and Cooke, 1930; Platou and Kohara, 1950).

With a intrauterine infection from cytomegalovirus, rubella, toxoplasmosis or a neonatal infection from herpes simplex and septic conditions with other bacteria, acute hemolytic

anemia may occur (Gill and Schwartz, 1972). Among these, sepsis especially in the newborn period may contribute to massive destruction which may cause anemia. Congenital syphilis is one of the causes of hemolytic anemia, and in our cases, all but one in the full-term infants and all premature infants showed compatible findings of regeneration of erythrocytes in the peripheral blood. There were also marked polychromasia and high levels of nucleated erythrocytes. With these findings, the patterns of anemia closely resembles the erythroblastic anemia as indicated by Barr *et al.*, (1963) and Whitaker *et al.* (1965).

The anemia also be due to abnormal erythrocyte fragility as indicated by Thurman (1960) and Whitaker *et al.* (1965). And as the bone marrow in the newborn period is hypofunction, this enhances the anemia along with hypersplenism. Since we did not examined the bone marrow with prolonged anemia, because of loss during follow-up, the possibility is hidden.

As shown in the results (Figure 1), hepatosplenomegaly and anemia have a close relationship and this explains that the anemia can result from hypersplenism as seen in mother report (Stokes *et al.*, 1944). Splenic enlargement, even though resulting from an infectious process, may become hyperfunctional and can produce anemia. Whitaker *et al.* (1965) noticed that the most pronounced anemia was seen with the largest spleen in two infants, but also pointed out that the hypersplenism is not the only cause, because one infant showed no increase in hemoglobin level after splenectomy. In our study, spleen decreased in size with penicillin therapy.

Barr *et al.* (1963) reported an aplastic type of anemia in congenital syphilis, and Whitaker *et al.* (1965) also reported generalized marrow hypoplasia with persistent anemia and low

reticulocyte count in one of nine patients. A bone marrow aspiration was done in our study showed normocellularity with erythroid hyperplasia, but this causative mechanism for developing anemia can not be excluded and more observations are needed.

Anemia in congenital syphilis might also result from nutritional deficiency (Piney, 1932), but Whitaker *et al.* (1965) denied this, as patients did not develop iron deficiency. We also did not notice significant hypochromia, microcytosis or megaloblastoid changes. There were also no megaloblastoid changes or iron lack on bone marrow examination.

The important causes of thrombocytopenia in the newborn and young infants are maternal antibodies, platelet sequestration during hemolytic disease of the newborn, and thrombocytopenia following replacement transfusion with stored blood, bacterial sepsis, protozoal infection and spirocheatal infections (Freiman and Super, 1966). Severe bleeding diathesis has also been described in young syphilitic infants (Barr *et al.*, 1963; Hochsinger, 1909; Freiman and Super, 1966; Josephs, 1936). Among these, Freiman and Super (1966) stated that syphilis was the

most important cause of thrombocytopenia during the first few months of life, reporting 15 syphilitic infants with complicating thrombocytopenia. Among the 15 infants, 10 infants showed a bleeding tendency, including visceral bleeding in two infants at necropsy and intracranial bleeding in one infant. The mechanism by which syphilis and infection in general causes thrombocytopenia is obscure. Freiman and Super (1966) postulated that the infection may either prevent the formation of megakaryocytes, or in some way interfere marrow metabolism and so prevent the normal development of the platelet precursors. but Kaplan (1959) explained that the responsible mechanism for thrombocytopenia during infection may be due to disturbance in platelet survivals rather than platelet production. The marrow in our study showed adequate platelet producing megakaryocytes, which reflects the above theory. Platelet levels return to normal during penicillin therapy, and this indicates that thrombocytopenia in some way alters platelet survival time.

The degree of leukocytosis cannot be related to the severity of disease (Whitaker *et al.*, 1965), and this may be due to the wide variety

Table 2. Initial Hemogram of Ten Syphilitic Infants

Case No.	Age days	Hb gs%	RBC $\times 10^5$	Hct %	Retic %	Plat. $\times 10^3$	WBC $\times 10^3$	Differential Count(%)						NRBC	Abs. Monocyte	
								Neutrophils			Lym	Mon	Eos			Bas
								Juv.	Stab.	Seg.						
1	60	6.2	2.80	18.0	3.5	136	22.5	4	5	15	38	36	2	1	3	8,100
2	15	15.5	4.61	47.2	1.6	391	13.5		3	27	53	16	3			2,160
3	2	18.8	6.27	59.1	3.2	192	17.1		1	65	31	3			6	513
4	1	13.3	3.93	40.1	3.7	330	16.4		1	50	39	9	1		25	1,476
5	1	20.4	5.51	62.2	5.4	152	16.	2	2	55	30	13			54	2,080
6	1	17.5	4.55	52.7	4.5	152	21.7		2	60	35	2	1		9	434
7	4	18.8	6.00	56.8	4.5	110	10.2			29	57	11	3		3	1,122
8	1	19.3	5.28	59.3	6.3	135	31.0	2	3	65	17	8	5	1	10	2,480
9	2	13.7	4.00	41.2	3.7	121	26.0	3	10	51	23	13			5	3,380
10	1	15.5	4.30	46.0	9.5	105	16.5	2	5	58	22	10	3		170	1,650

of the total leukocyte count, as well as patterns of differential counts in normal infants, especially in the first week of life, which make it difficult to evaluate the diseased child. Kove *et al.* (1957) wrote that in the majority of cases, absolute lymphocytosis was noticed with congenital syphilis, and in contrast, a marked shift to myelocytosis was also reported (Barr *et al.*, 1963). Some showed constant irritation of bone marrow, characterized by an outpouring of characteristic leukocytes including eosinophils (1909). Kim *et al.* (1976) showed absolute monocytosis in 10 cases in their unpublished report (Table 2). Usually there are wide variations of differential count from lymphocytosis to a myeloid reaction. We found relative lymphocytosis, but this also did not reflect the severity of the infection.

The jaundice was mainly due to unconjugated bilirubin in 6 infants, and in the other 8 infants, the jaundice was due to conjugated as well as unconjugated bilirubin. With these results, hemolysis also can not fully explain the above mentioned anemia. In severe infections, toxic liver damage with regurgitation jaundice may precede by a hemolytic or retention phase (Hamilton and Sass-Kortsak, 1863). This may be due to the typical histologic features of liver as shown by extramedullary hematopoiesis in the sinusoids and inflammatory cells diffusely around the blood vessels and bile ducts in the portal triad (Bernstein and Brown, 1962), as in our infant. The jaundice in congenital syphilis can result from multiple factors; hemolysis, spirochetal hepatitis, hepatic immaturity, and possible stasis in the bile ducts (Whitaker *et al.*, 1965).

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