Infection Associated Hemophagocytic Syndrome : A Report of 50 Children

VANDEE NINGSANOND, M.D.*

Abstract

Fifty children were diagnosed with infection associated hemophagocytic syndrome (IAHS) over the 10 year period from January 1988 through December 1997 at Queen Sirikit National Institute of Child Health, Thailand. Their ages ranged from 2 months to 14 years (mean 4.14 years). There was no difference in sex. Bacterial, mycobacterial, viral, fungal and protozoa were the associated infections in some of these patients. Supportive with specific therapy for the underlying disease was administered aggressively in all patients. Intravenous immuneglobulin (IVIG) was given in 8 patients. Thirty-five patients (70%) died, mostly as a result of coagulopathy with multiple organ failure and opportunistic infections. Two patients developed acute lymphoblastic leukemia 25 days and 3 months after recovering from IAHS.

Key word : Hemophagocytic Syndrome, Infection, Report of 50 Children

NINGSANOND V
J Med Assoc Thai 2000; 83: 1141-1149

Hematologic abnormalities complicating childhood infectious diseases have been recognized as a common feature for many decades. In 1979, Risdall et al described 19 patients with a distinct clinical syndrome which occurred in a setting of immunosuppression with viral infections and named this disorder virus associated hemophagocytic syndrome (VAHS)[1]. This syndrome is characterized by high fever, constitutional symptoms, lymphadenopathy, hepatosplenomegaly, skin rash, pancytopenia, liver function abnormalities, and coagulopathies. The pathologic hallmark of VAHS consists of benign histiocytic proliferation and striking phagocytosis of red blood cells, white blood cells and platelets by histiocytes in bone marrow, lymph nodes and in some cases liver, spleen[2,3] and cere-

* Hematology Division, Department of Pediatrics, Queen Sirikit National Institute of Child Health, Bangkok 10400, Thailand.

brospinal fluid[4,5]. Since then, many reports on this condition have been published[6-8] and other infectious pathogens such as bacteria[9-11], mycobacteria[12,13], and parasites[2] have been identified to be associated with this syndrome. Therefore, Risdall considered and renamed this condition infection associated hemophagocytic syndrome (IAHS)[14] which is still used nowadays. However, most of these cases appeared in the literature as short case reports and mainly in adult patients. In this report, we describe the clinical features, laboratory findings, outcome and some possible infectious causes of 50 children with IAHS at Queen Sirikit National Institute of Child Health (Children's Hospital), Bangkok, Thailand over a period of 10 years.

MATERIAL AND METHOD

Queen Sirikit National Institute of Child Health (formerly Children's Hospital) is a 538 beds, government administered, referral and tertiary care hospital located in the center of metropolitan Bangkok. There are approximately 280,000 annual outpatients and 10,000 inpatients each year.

All patients' records with the discharge diagnosis of IAHS hospitalized during the time period of January 1988 through December 1997 at Queen Sirikit National Institute of Child Health were reviewed and analyzed for their clinical features, laboratory findings and outcomes. The diagnostic criteria of IAHS are (1) unexplained cytopenia involving at least two cell lines in the peripheral blood smear, and (2) identified proliferation of mature histiocytes with hemophagocytosis in the bone marrow. The patients' records which met the inclusion criteria were analyzed for age at presentation, sex, clinical features, laboratory studies especially bone marrow findings, the possible infectious causes, treatment and outcome. Statistical analysis was done by using the chi-square test, student *t* test, and Fisher's exact test, comparing the clinical and laboratory data between 2 groups of patients, survival and non-survival.

RESULTS

Clinical Features

During the 10 year period of this study, there were 50 patients with IAHS. Their ages ranged from 2 months to 14 years with the median age of 28 months (mean 4.14 years). The age of twenty-four cases (48%) were below 24 months, while nine cases (18%) were between 24 and 39 months and seventeen cases (34%) were more than 60 months. The peak incidence of IAHS occurred during the second year of life. The ratio of male to female was 1:1.

The mean yearly incidence of this syndrome was five cases with a range of 2 cases in 1993 to 11 cases in 1991. The clinical features of 50 patients are summarized in Table 1. The duration of the presenting symptoms of the illness in these patients was highly variable and ranged from days to months (2 days to 2.5 months). Fever was the most consistent feature (100%) in all patients with a range duration of 2 to 60 days (median 10 days)

Table 1. Clinical features of 50 IAHS patients.

Clinical features	Non- survivor N = 35	%	Survivor N = 15	%	Total N = 50	%	p - value
Mean Age - year (SD)	4.13	3.8	3.8	4.07	4.14		0.79
range age	2 mo. - 12 yr		4 mo. - 14 yr.		2 mo. - 14 yr.		-
Male : Female	18:17		6 : 9		1 : 1		0.46
Fever	35	100	15	100	50	100	1
Constitutional symptoms	32	91.4	15	100	47	94	0.90
Rash	6	17.1	1	6.6	7	14	0.66
Bleeding	16	45.7	7	46.6	23	46	0.95
Lymphadenopathy	14	40	3	20	17	34	0.21
Hepatomegaly	29	82.8	10	66.7	39	78	0.27
Splenomegaly	30	85.7	12	80	42	84	0.68
Pallor	24	68.5	10	66.6	34	68	0.9
Jaundice	18	51.4	4	26.6	22	44	0.11

before the diagnosis was established. Forty-seven patients (94%) had moderate to severe constitutional symptoms which included malaise, anorexia, gastrointestinal symptoms, weight loss, weakness and respiratory complaints. The other common symptoms and signs were splenomegaly (84%), hepatomegaly (78%), pallor (68%), bleeding (46%), jaundice (44%), lymphadenopathy (34%), and skin rash (14%). The fatality rate was 70 per cent. There was no statistically significant difference (P>0.05) in clinical manifestations between survival and non-survival groups.

Laboratory Findings

The frequencies of various laboratory abnormalities are listed in Table 2. Anemia, thrombocytopenia and leukopenia occurred in 100 per cent, 92 per cent and 68 per cent respectively. All 50 patients had significant decrease of at least 2 hematologic cell lines while 31 patients (62%) had pancytopenia. Neutropenia (absolute neutrophil $<1,500/mm^3$) was found in 34 patients (68%). The coagulation abnormalities, defined as prolonged prothrombin time (>12 sec) and prolonged partial thromboplastin time (>37 sec) were found in 100 per cent and 96.8 per cent respectively. The elevation of serum AST and ALT were found in 87.7 per cent and 69.4 per cent, while the elevation of serum bilirubin was found in 86.7 per cent. All of the laboratory features were not statistically significantly different between the survival and non-survival groups except serum ALT and serum bilirubin which were significantly elevated in the non-survival group (p <0.05).

Table 2. Laboratory features of 50 IAHS patients.

Laboratory features	Non- survivor N = 35	%	Survivor N = 15	%	Total N = 50	%	p - value
Pancytopenia	24/35	58.6	7/15	46.7	31/50	62	0.14
Anemia (Hct < 33%)	35/35	100	15/15	100	50/50	100	1
Leukopenia (WBC < 4500/mm^3)	26/35	74.3	8/15	53.3	34/50	68	0.14
Thrombocytopenia (Plts < 100,000/mm^3)	32/35	91.4	13/15	86.7	45/50	92	0.63
Neutropenia (N < 1,500/mm^3)	26/35	74.3	8/15	53.3	34/50	68	0.14
Prolonged PT (> 12 sec)	25/25	100	6/6	100	31/31	100	1
Prolonged PTT (> 37 sec)	25/25	100	5/6	83.3	30/31	96.8	0.61
Elevated AST (>40 unit)	32/35	91.4	11/14	78.5	43/49	87.7	0.33
Elevated ALT (>35 unit)	28/35	80	6/14	42.8	34/49	69.4	0.01
Elevated bilirubin (>0.5 mg / dl)	30/32	93.7	9/13	69.2	39/45	86.7	0.049

PT = Prothrombin time
PTT = Partial thromboplastin time
AST = L - aspartate - 2 - oxaloglutarate aminotransferase (SGOT)
ALT = L - alanine - 2 - oxaloglutarate amino transferase (SGPT)

Table 3. Bone Marrow features of 50 IAHS patients.

Bone Marrow features	Non- survivor N = 35	%	Survivor N = 15	%	Total N = 50	%	p - value
Hemophagocytosis	35	100	15	100	50	100	1.0
Histiocytic hyperplasia	35	100	15	100	50	100	1.0
Hypocellularity	15	42.8	8	53.3	23	46	0.5
Hypercellularity	16	45.7	6	40	22	44	0.71
Decreased megakaryocyte	17	48.5	6	40	23	46	0.58
Normal megakaryocyte	12	34.2	5	33.3	17	34	0.95
Myeloid hypoplasia	16	45.7	5	33.3	21	42	0.42
Erythroid hypoplasia	6	17.1	4	26.6	10	20	0.46*
Maturation arrest of myeloid series	8	22.8	1	6.6	9	18	0.25*

* Fisher's exact test

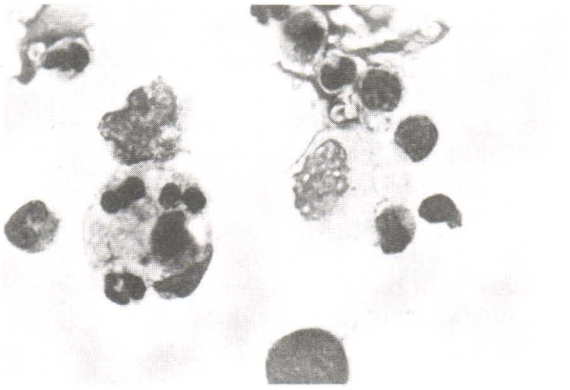

Fig. 1. Bone marrow smear showing benign histiocytic proliferation with hemophagocytosis (Wright stain, original magnification x 400).

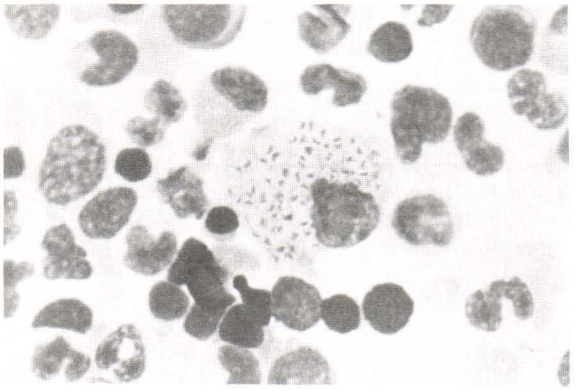

Fig. 2. Phagocytosis of *Penicillium marneffei* by bone marrow histiocytes in patient who had underlying acquired immunodeficiency syndrome (Wright stain, original magnification x 400).

The major bone marrow findings are summarized in Table 3. The histiocytic hyperplasia and hemophagocytosis of various hematopoietic cells were the consistent hallmark findings in all 50 patients (Fig. 1). The varying degree of bone marrow abnormalities such as hypocellularity, hypercellularity, decreased megakaryocytes, normal megakaryocytes, myeloid hypoplasia, erythroid hypoplasia and maturation arrest of myeloid series were not statistically significantly different between the survival and non-survival group (P>0.05). Malarial pigment was presented within the cytoplasm of the bone marrow histiocyte in 4 patients who had the ring form of *Plasmodium falciparum* in peripheral blood smear. There were numerous extra-cellular and intracellular *Penicillium marneffei* in several histiocytes of one patient who had underlying acquired immunodeficiency syndrome (Fig. 2).

The bacterial cultures were tested in all patients and viral studies were tested in 14 patients, the possible identifiable infectious causes were documented in only 16 patients (32%). There were 5 viral infections (dengue virus 1, human immunodeficiency virus 4), 7 bacterial infections (*Escherichia coli* 2, *Pseudomonas aeruginosa* 2, *Klebsiella pneumoniae* 2, *Citrobacter spp.* 1), 1 *Mycobacterium tuberculosis*, 2 fungal infections (*Histoplasma capsulatum* 1, *Penicillium marneffei* 1) and 4 protozoan (*Plasmodium falciparum*). Of these, 5 patients were probably infected with more than one pathogen. The infectious etiology could not be identified by cultures or serologic tests in another 34 patients.

Non-infectious underlying diseases were found in 3 patients. They were 1 retinoblasma, 1 Down's syndrome and 1 β - thalassemia/ Hb E disease.

Management and Outcome

Fifteen patients (30%) survived after various regimens of antimicrobial therapy and supportive care. The clinical symptoms and laboratory abnormalities were improved within 1 to 10 weeks after treatment. There was no recurrences of this clinical syndrome but 2 patients developed acute lymphoblastic leukemia at 25 days in one case and the other at 3 months after they recovered from IAHS. The other 35 patients (70%) died in spite of the aggressive antimicrobial therapy and supportive care including blood components transfusions. The duration from diagnosis to death varied from a few days to 9 weeks. The major causes of death were sepsis, hemorrhage and multiple organ failure. In this non-survival group, 8 patients received intravenous immuneglobulin (IVIG) with the doses varying from 500 mg/ kg/day intravenously for 5 days (4 cases) to 2 g/kg/dose for 1 day (4 cases) but unfortunately all of them died within 3 weeks after immunotherapy. Exchange transfusion was also performed in 2 patients and both of them died 1 day after treatment. Other treatments, such as steroid and cytotoxic drugs, were not applied in any patients.

DISCUSSION

According to our medline search in the year 2000, this is probably the largest reported series of pediatric IAHS in Thailand and also throughout Asia. This clinical syndrome was originally recognized in 1979 by Risdall *et al*, who described the proliferation of non-malignant histiocytes with prominent hemophagocytosis in bone marrow that differed from the previous report of malignant histiocytosis[15]. The incidence of this syndrome in many countries throughout the world is unknown, but we expect that, it is not uncommon especially in tertiary care centers. The yearly incidence of IAHS in our institute is around 5 cases (0.05% of total admissions) which is similar to the experience of Reiner *et al* in 1988[16]. There is no sex difference in our report while it is distinguishable from many reports that males are slightly preponderant[16-19]. The distribution of age of this syndrome in former reports ranged from newborn [18] to 84 years old[19], but in our study (only in a pediatric setting) the age ranged from 2 months to 14 years with the median age of 28 months. This might be the common age for many viral and bacterial infections among Thai children, which might play an important role in the pathogenesis of this syndrome.

The common presenting clinical features in our 50 patients are the same as many reports including fever which is the most consistent feature in all patients, weakness, fatigue, anorexia, gastrointestinal symptoms, malaise and bleeding. The duration of these presenting symptoms is highly variable ranging from days to months[16] which is the same as in our experience. The dermographic data, clinical manifestations, laboratory and bone marrow findings are not different between survival and non-survival groups in this series except the serum ALT and serum bilirubin level which were significantly elevated in the non-survival group and might reflect the fulminant course of this syndrome.

The possible 19 infectious agents were documented in 16 of 50 IAHS patients (32%) whereas 5 patients were probably infected with more than one organism. Originally, this syndrome was reported as "virus associated hemophagocytic syndrome" (VAHS) by Risdall *et al* in 1979[1] because most of the causative organisms were viruses such as herpes virus, adenovirus and cytomegalovirus. Subsequently, many investigators reported the broad spectrum of this syndrome with other viruses (Ebstein-Barr virus[3,6,8,20-25], herpes group virus[4], parvovirus B_{19}[26,27], dengue virus[28], HIV[29-31]), bacteria (*Escherichia coli*[14,19], enteric gram-negative bacilli[16], *Streptococcus pneumoniae*[14], *Staphylococcus aureus* [16], *Hemophilus influenzae*[16], *Mycoplasma pneumoniae*[32], *Brucella melitensis*[9-11], *Salmonella typhi*[33,34]), *Mycobacterium tuberculosis*[12,13, 35-38], fungi (*Histoplasma*[16], *Candida albican* [16], *Crytococcus neoforman*[16], *Aspergillus fumigatus*[31]), rickettsia[19], parasites (*Leishmania donovani*[2], *Babesia microti*[39], protozoa (*Plasmodium falciparum*[40]). Infectious agents in our patients were identified by microbiologic, serologic or histologic techniques. Nine gram negative bacilli bacteria were isolated from blood, one *M. tuberculosis* was isolated from bone marrow and lymph node, one dengue virus and four HIV were confirmed by serology, one histoplasma was confirmed by bone marrow examination and skin biopsy and one patient with *Penicillium marneffei* was demonstrated in bone marrow aspiration. Malarial pigment and gametocyte of *Plasmodium falciparum* were identified in bone marrow examination of 4 IAHS patients. The underlying microbial organisms might be different from place to place regarding the geographic prevalence of many infections. HIV infection was confirmed in 4 of 13 patients (31%) and three of them were complicated by disseminated histoplasmosis, citrobacter septicemia and *Penicillium marneffei* infection, respectively. The infectious etiology of the other 34 patients in our series could not be identified in spite of aggressive investigations. Although, the pathophysiology of IAHS remains unknown some authors have postulated that it is probably the result of infection induced defect in immune regulation such as excessive cytokine production and abnormal T-cell function[51-56].

Many reports described patients with malignant lymphoma[19,41-49], acute lymphoblastic leukemia[7,44] and Hodgkin's disease[50] associated with hemophagocytic syndrome. All these patients developed this syndrome while still receiving cytotoxic therapy for their malignancies, but in this report, two patients developed acute lymphoblastic leukemia following the recovery period of IAHS despite their clinical features, laboratory results and bone marrow findings having already returned to normal. These two patients were resis-

tant to conventional chemotherapy and both died a few months after the established diagnosis.

At present, there is no specific treatment for IAHS, but from previous reports, many therapeutic approaches such as splenectomy[2,3,26], administration of corticosteroid[4], acyclovir[4,57], vinka alkaloid, cyclosporin A[24,57,58], etoposide [4,5,18,24,36], withdrawal of immunosuppressive drugs[1], and only clinical support[8,20,28] have been tried with limited efficacy. Recently, there were some reports showing the success of therapy with intravenous immuneglobulin[57,59-63] (IVIG). We treated 8 of our patients with various dosages of IVIG, but unfortunately, all of them died with fulminant course of the disease. Nevertheless specific antimicrobial therapy and supportive care play an important role in the survival rate of many patients with IAHS[9,14,19,33,34].

Though this syndrome is self-limited with resolution of the clinical and laboratory abnormalities within several weeks, the mortality rate from the literature is still high varying from 20 to 100 per cent[1,16,17,19]. In our study, the mortality rate was as high as 70 per cent which reflects the unsolved complex problems in our IAHS patients. The possible causes of death among our patients were severe hemorrhage, septicemia and multiorgan failure that is very similar to many reports[6,16-19,21,23,24]. Fifteen (30%) of our patients improved with either specific antimicrobial therapy or supportive care without IVIG.

In conclusion, IAHS is not a rare clinical entity in the setting of a tertiary pediatric care hospital. The differential diagnosis of IAHS should be included with patients who present with fever, hepatosplenomegaly, lymphadenopathy and pancytopenia. Recognition of this syndrome is therefore important because the early definite diagnosis and appropriate treatment will create a better clinical outcome.

(Received for publication on April 21, 2000)

REFERENCES

1. Risdall RJ, Mckenna RW, Nesbit ME, et al. Virus associated haemophagocytic syndrome: a benign histiocyte proliferation distinct from malignant histiocytosis. Cancer 1979; 44: 993 – 1002.
2. Matzner Y, Behar A, Beeri E, et al. Systemic Leishmaniasis mimicking malignant histiocytosis. Cancer 1979; 43: 398 – 402.
3. Ross CW, Schnitzer B, Weston BW, Hanson CA. Chronic active Epstein-Barr virus infection and virus – associated hemophagocytic syndrome. Arch Pathol Lab Med 1991; 115: 470 – 4.
4. Olson NY, Olson LC. Virus – associated hemophagocytic syndrome: relationship to herpes group virus. Pediatr Infect Dis 1986; 5: 369 – 73.
5. Hirst W, Vergani GM, Ball C, et al. Clinicomorphological feature and treatment of childhood hemophagocytic syndrome. Br J Hematol 1991; 77: suppl 1 – 16.
6. Wilson ER, Malluh A, Stagno S, Crist WM. Fatal Epstein – Barr virus – associated hemophagocytic syndrome. J Pediatr 1981; 98: 260 – 2.
7. Yin JAL, Kumaran TO, Marsh GW, et al. Complete recovery of histiocytic medullary reticulosis – like syndrome in a child with acute lymphoblastic leukemia. Cancer 1983; 51: 200 – 2.
8. Reisman RP, Greco MA. Virus – associated hemophagocytic syndrome due to Epstein – Barr virus. Hum Pathol 1984; 15: 290 – 3.
9. Zuazu J P, Duran JW, Julia AF. Hemophagocytosis in acute brucellosis. N Eng J Med 1979; 301: 1185 – 6.
10. Moreno SM, Guzman OS, Bernado – de – Quiros J, et al. Pancytopenia due to hemophagocytosis in patients with brucellosis: A report of four cases. J Infect Dis 1983; 147: 445 – 9.
11. Kokkini G, Giotaki HG, Moutsopoulos HM. Transient hemophagocytosis in Brucella melitensis infection. Arch Pathol Lab Med 1984; 108: 213 – 6.
12. Barnes N, Bellamy D, Ireland R, et al. Pulmonary tuberculosis complicated by haemophagocytic syndrome and rifampicin – induced tubulointerstitial nephritis. Br J Dis Chest 1984; 78: 395 – 403.
13. Weintraub M, Siegman – Igra Y, Josiphov J, et al. Histiocytic hemophagocytosis in miliary tuberculosis. Arch Intern Med 1984; 144: 2055 – 7.
14. Risdall RJ, Brunning RD, Hernadez JI, et al. Bacteria – associated hemophagocytic syndrome. Cancer 1984; 54: 2968 – 72.
15. Warnke RA, Kim H, Dorfman RF. Malignant histiocytosis (Histiocytic medullary reticulosis). Clinicopathology study of 29 cases. Cancer 1975; 35: 215 – 30.
16. Reiner AP, Spivak JL. Hematophagic histiocytosis.

A report of 23 new patients and a review of the literature. Medicine 1988; 67: 369 – 88.
17. Chan JKC, NG CS, Law CK, et al. Reactive hemophagocytic syndrome: A study of 7 fatal cases. Pathology 1987; 19: 43 – 50.
18. Chen RL, Su IJ, Lin KH, et al. Fulminant childhood hemophagocytic syndrome mimicking histiocytic medullary reticulosis. Am J Clin Pathol 1991; 96: 171 – 6.
19. Wong KF, Chan JKC. Reactive hemophagocytic syndrome – A clinicopathologic study of 40 patients in an oriental population. Am J Med 1992; 93: 177 – 80.
20. Sullivan JL, Woda BA, Herrod HG, et al. Epstein – Barr virus – associated hemophagocytic syndrome: virological and immunopathological studies. Blood 1985; 65: 1097 – 104.
21. Mroczek EC, Weisenburger DD, Grierson HL, et al. Fatal infectious mononucleosis and virus – asso ciated hemophagocytic syndrome. Arch Pathol Lab Med 1987; 111: 530 – 5.
22. Kawaguchi H, Miyashita T, Herbst H, et al. Epstein – Barr virus – infected T lymphocytes in Epstein – Barr virus – associated hemophagocytic syndrome. J Clin Invest 1993; 92: 1444 – 50.
23. Kikuta H, Sakiyama Y, Matsumoto S, et al. Fatal Epstein – Barr virus – associated hemophagocytic syndrome. Blood 1993; 82: 3259 – 64.
24. Okano M, Gross TG. Epstein – Barr virus – associated hemophagocytic syndrome and fatal infectious mononucleosis. Am J Hematol 1996; 53: 111 – 5.
25. Wong KF, Chan JK, Lo ES, Wong CS. A study of the possible etiologic association of Epstein – Barr virus with reactive hemophagocytic syndrome in Hong Kong Chinese. Hum Pathol 1996; 27: 1239 – 42.
26. Boruchoff SE, Woda BA, Pihan GA, et al. Parvovirus B19 – associated hemophagocytic syndrome. Arch Intern Med 1990; 150: 897 – 9.
27. Muir K, Todd WTA, Watson WH, Fitzsimons E. Viral – associated hemophagocytosis with parvovirus – B19 – related pancytopenia. Lancet 1992; 339: 1139 – 40.
28. Wong KF, Chan JKC, Chan JCW, et al. Letter to the editor: Dengue virus infection – associated hemophagocytic syndrome. Am J Hematol 1991; 38: 339 – 40.
29. Lortholary A, Raffi F, Aubertin P, et al. HIV – associated haemophagocytic syndrome. Lancet 1990; 336: 1128.
30. Rule S, Reed C, Costello C. Fatal Haemophagocytic syndromes in HIV – antibody positive patient. Br J Hematol 1991; 79: 127.
31. Dalle JH, Dollfus C, Courpotin C, et al. Human immunodeficiency virus – associated hemophagocytic syndrome in children. Pediatr Infect Dis 1994; 13: 1159.
32. Gill K, Marrie TJ. Hemophagocytosis secondary to Mycoplasma pneumonia infection. Am J Med 1987; 82: 668 – 70.
33. Fame TM, Engelhard D, Riley HD. Hemophagocytosis accompanying typhoid fever. Pediatr Infect Dis 1986; 5: 367 – 9.
34. Udden MM, Banez E, Sears DA. Bone marrow histiocytic hyperplasia and hemophagocytosis with pancytopenia in typhoid fever. Am J Med Sci 1986; 291: 396 – 400.
35. Campo E, Condom E, Miro M–J, et al. Tuberculosis – associated hemophagocytic syndrome. Cancer 1986; 58: 2640 – 5.
36. Monier B, Fauroux B, Chevalier JY, et al. Miliary tuberculosis with acute respiratory failure and histiocytic hemophagocytosis. Successful treatment with extracorporeal lung support and epipodophyllotoxin VP 16 – 213. Acta Pediatr 1992; 81: 725 – 7.
37. Lam KY, NG WF, Chan ACL. Case report. Miliary tuberculosis with splenic rupture: A fatal case with hemophagocytic syndrome and possible association with long standing sarcoidosis. Pathology 1994; 26: 493 – 6.
38. Undar J, Karpuzoglu G, Karadogan I, et al. Tuberculosis – associated haemophagocytic syndrome: A report of two cases and a review of the literature. Acta Haematol 1996; 96: 73 – 8.
39. Auerbach M, Haubenstock A, Soloman G. Systemic babesiosis. Another cause of the hemophagocytic syndrome. Am J Med 1986; 80: 301 – 3.
40. Ohno T, Shirasaka A, Sugiyama T, Furukawa H. Hemophagocytic syndrome induced by Plasmodium falciparum malaria infection. Int J Hematol 1996; 64: 263 – 6.
41. Kadin ME, Kamoun M, Lamberg J. Erythrophagocytic T lymphoma. A clinicopathologic entity resembling malignant histiocytosis. N Eng J Med 1981; 304: 648 – 53.
42. Jaffe ES, Costa J, Fauci AS, et al. Malignant lymphoma and erythophagocytosis simulating malignant histiocytosis. Am J Med 1983; 75: 741 – 9.
43. NG CS, Chan JKC, Cheng PNM, Szeto SC. Nasal T – cell lymphoma associated with hemophagocytic syndrome. Cancer 1986; 58: 67 – 71.
44. Liang D, Chu ML, Shih C. Reactive histiocytosis in acute lymphoblastic leukemia and non – Hodgkin's lymphoma. Cancer 1986; 58: 1289 – 94.
45. Falini B, Pileri S, De Solas I, et al. Peripheral T – cell lymphoma associated with hemophagocytic syndrome. Blood 1990; 75: 434 – 44.
46. Wong KF, Chan JKC, Ng CS, et al. Anaplastic large cell Ki – 1 lymphoma involving bone

marrow: Marrow findings and association with reactive hemopha-gocytosis. Am J Hematol 1991; 37: 112 – 9.
47. Yao M, Cheng AL, Su IJ, et al. Cliniciopathiological spectrum of haemophagocytic syndrome in Epstein – Barr virus – associated peripheral T – cell lymphoma. Br J Haematol 1994; 87: 535 – 43.
48. Nakajima A, Abe T, Takagi T, et al. Two cases of malignant lymphoma with initial symptoms like orbital cellulitis and complicated by hemophagocytosis. Nippon Ganka Gakkai Zasshi 1996; 100: 641 – 9.
49. Yamada K, Katoh K, Okuyama M. Diffuse B – cell lymphoma associated with hemophagocytic syndrome. Rinsho Ketsueki 1996; 37: 161 – 4.
50. Kornan LY, Smith JR, Landaw SA, Davey FR. Hodgkin's disease: Intramedullary phagocytosis with pancytopenia. An Intern Med 1979; 91: 60 – 1.
51. Daum GS, Sullivan JL, Ansell J, et al. Virus – associated hemophagocytic syndrome: identification of an immunoproliferative precursor lesion. Hum Pathol 1987; 18: 1071 – 4.
52. Komp DM, McNamara J, Buckley P. Elevated soluble interleukin – 2 receptor in childhood hemophagocytic histiocytic syndromes. Blood 1989; 73: 2128 – 32.
53. Imashuku S, Hibi S. Cytokines in haemophagocytic syndrome. Br J Haematol 1991; 77: 438 – 40.
54. Owen G, Webb DKH. Evidence of clonality in a child with haemophagocytic lymphohistiocytosis. Br J Haematol 1995; 89: 681 – 2.
55. Ladisch S, Jaffe ES. The histiocytoses. In: Pizzo, P. A. & Poplack, D. G. (eds): Principles and practice of pediatric oncology. Philadelphia PA. Lippincott 1997; 615 – 31.
56. Akashi K, Hayashi S, Gondo H, et al. Involvement of interferon – ϒ and macrophage colony – stimulating factor in pathogenesis of haemophagocytic lymphohistiocytosis in adults. Br J Haematol 1994; 87: 243 – 50.
57. Watson HG, Goulden NJ, Manson LM, et al. Virus – associated haemophagocytic syndrome: further evidence for a T – cell mediated disorder. Br J Haematol 1994; 86: 213 – 5.
58. Oyama Y, Amano T, Hirakawa K, et al. Haemophagocytic syndrome treated with cyclosporin A: A T cell disorder? Br J Haematol 1989; 73: 276 – 8.
59. Goulder P, Seward D, Hatton C. Intravenous immunoglobulin in virus associated hemophagocytic syndrome. Arch Dis Child 1990; 65: 1275 – 7.
60. Freeman B, Rathore MH, Salman E, et al. Intravenously administered immune globulin for the treatment of infection – associated hemophagocytic syndrome. J Pediatr 1993; 123: 479 – 81.
61. Fort DW, Buchanan GR. Treatment of infection – associated hemophagocytic syndrome with immune globulin. J Pediatr 1994; 124: 332.
62. Gill DS, Spencer A, Cobcroft RG. High – dose gamma – globulin therapy in the reactive haemophagocytic syndrome. Br J Haematol 1994; 88: 204 – 6.
63. Chen RL, Lin KH, Lin DT, et al. Immunomodulation treatment for childhood virus – associated haemophagocytic lymphohistiocytosis. Br J Haematol 1995; 89: 282 – 90.

ภาวะติดเชื้อที่สัมพันธ์กับกลุ่มอาการฮีโมฟาโกซัยติค รายงานผู้ป่วยเด็ก 50 ราย

*วันดี นิงสานนท์, พ.บ.**

ระหว่างปี พ.ศ. 2531 ถึง พ.ศ. 2540 มีผู้ป่วยเด็ก 50 รายได้รับการวินิจฉัยว่าเป็น infection associated hemophagocytic syndrome ที่สถาบันสุขภาพเด็กแห่งชาติมหาราชินี (โรงพยาบาลเด็ก) อายุเฉลี่ย 4.14 ปี (2 เดือน ถึง 14 ปี) พบในเพศหญิงเท่ากับเพศชาย เชื้อที่พบร่วมกับกลุ่มอาการนี้ได้แก่ เชื้อแบคทีเรีย เชื้อไวรัส เชื้อรา และเชื้อมาลาเรีย ผู้ป่วยทุกรายได้รับการรักษาด้วยยาปฏิชีวนะ ส่วนประกอบของเลือดต่างๆ ร่วมกับการรักษาแบบประคับประคองอย่างเต็มที่ มีผู้ป่วย 8 รายที่ได้รับการรักษาด้วย intravenous immuneglobulin (IVIG) อัตราตาย 70% ส่วนใหญ่เป็นผลมาจากความผิดปกติในการแข็งตัวของเลือดร่วมกับการทำงานของอวัยวะต่างๆล้มเหลว และจากเชื้อฉวยโอกาส มีผู้ป่วย 2 ราย หลังจากหายจากกลุ่มอาการนี้แล้ว เป็นมะเร็งเม็ดโลหิตขาวแบบเฉียบพลันในเวลา 25 วันและ 3 เดือน ตามลำดับ

คำสำคัญ : กลุ่มอาการฮีโมฟาโกซัยติค, ภาวะติดเชื้อ, รายงานผู้ป่วยเด็ก 50 ราย

วันดี นิงสานนท์
จดหมายเหตุทางแพทย์ ฯ 2543; 83: 1141–1149

* งานโลหิตวิทยา, สถาบันสุขภาพเด็กแห่งชาติมหาราชินี, กรุงเทพ ฯ 10400