文献 6)　Maruyama K., et al. : Pediatrics International, Vol.41, P82-89, (1999).

Pediatrics International (1999) **41**, 82–89

Original Article

Prenatal and postnatal histories of very low birthweight infants who developed hepatoblastoma*

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Abstract

Background: Hepatoblastoma in children of very low birthweight (< 1500 g) is increasing in Japan and this has suggested the presence of either a genetic or environmental etiology. This study was aimed at revealing common prenatal and postnatal histories, including family history of hepatoblastomas in children of very low birthweight.
Methods and Results: The medical records of 15 patients, nine boys and six girls, were reviewed. The patients were diagnosed at the age of 6–77 months (median 16 months). Their birthweight ranged from 560 to 1380 g (median 826 g) and the gestational age was 23–33 weeks (median 25 weeks). No parents were exposed to any occupational risk factors and there were no characteristic features in the parents' history or the maternal reproductive history, although one patient was born to a mother who had taken a contraceptive before she got pregnant with the patient as a result of *in vitro* fertilization. A ventricular septal defect and an atresia of the external auditory canal were congenital anomalies seen in the patients, but congenital anomalies associated with hepatoblastoma were not seen. Early postnatal illnesses included respiratory distress syndrome in six patients, symptomatic patent ductus arteriosus in three patients, chronic lung disease in seven patients, cytomegalovirus hepatitis in one patient and cholelithiasis in one patient. Oxygen therapy was given to 13 patients for a period of 4–508 days (median 112 days) and lengths of oxygen therapy and assisted ventilation were significantly longer in patients with a stage IIIB or IV tumor than those with a stage II or IIIA tumor ($P = 0.0040$ and 0.0190, respectively). Furosemide was used in 13 patients for a period of 6–460 days (median 88 days) and the length of the treatment was also significantly longer in patients with advanced tumors ($P = 0.0420$). Among the patients at 23–25 weeks of gestation, these treatments tended to be longer in patients with a stage IIIB or IV tumor than those with a stage II or IIIA tumor.
Conclusions: These results suggest the presence of an environmental etiology, rather than a genetic one, which is responsible for the development of hepatoblastoma in children of very low birthweight. Close monitoring of the children after being discharged from the neonatal intensive care unit is essential and a case-control study is necessary to identify risk factors for hepatoblastoma in children of very low birthweight.

Key words　hepatoblastoma, postnatal history, prenatal history, very low birthweight.

Hepatoblastoma is the most common malignant hepatic tumor in children. Morphologically, epithelial components of hepatoblastoma resemble differentiating hepatocytes at different stages of normal development and the tumors are classified into fetal, embryonal and anaplastic type tumors.[1] While hepatoblastoma is believed to be an embryonal tumor which results from developmental disturbances during organogenesis, little is known about the etiologies of the tumor. Beckwith–Wiedemann syndrome, hemihypertrophy, trisomy 18 syndrome and familial adenomatous polyposis are associated with the tumor and genetic and molecular studies are focused on the identification of the genes responsible for the abnormalities and hepatoblastoma.[2,3] Germline mutation in the 5′ end of the adenomatous polyposis coli gene, which is located on the long arm of chromosome 5 in band q21, was found to be associated with hepatoblastoma.[4] The proportion of patients with a congenital anomaly, however, is only approximately 6% and the majority of patients are not associated with congenital anomalies.[5] However, there are some possible connections between oral contraceptive intake, alcohol abuse during pregnancy, hormonal treatment for sterility, parental occupational exposure to metals, petroleum products and paints or pigments and the occurrence of hepatoblastoma.[6–9]

In the previous paper, we analyzed the data in the Japan Children's Cancer Registry to examine the impression that a

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Received 3 July 1998; accepted 14 August 1998.

*Presented in part at the 29th Meeting of the International Society of Pediatric Oncology, Istanbul, Turkey, September 23-27, 1997.

文献 6)　Maruyama K., et al. : Pediatrics International, Vol.41, P82-89, (1999).

considerable number of hepatoblastomas had developed in premature infants and showed that hepatoblastoma in children of very low birthweight (< 1500 g) was increasing in Japan.[10] There was a significant linear trend toward an increase in the percentage of the patients with hepatoblastoma, which was 7.6% in the 5 year period from 1990 to 1994. The incidence of live premature babies of very low birthweight is 0.5–0.6% of all live births.[11] As the phenomenon was specific to hepatoblastoma, it was suggested that there were some reasons for the increase, apart from the simple increase in the number of premature infants who survive. In addition, the increase was attributed to the significant increase in the percentage of patients of extremely low birthweight (< 1000 g) and the incidence peak in the number of patients in the birthweight range of < 1000 g was separated from the second peak in the range of 2500–4000 g. These epidemiological observations have suggested that etiological factors, either genetic or environmental, may be present.

As the next step in the investigation, we have analyzed the patients' data and have clarified the characteristics of hepatoblastomas in children of very low birthweight. Through reviewing the surgical and pathologic aspects of the tumors, it has become evident that hepatoblastomas in children of very low birthweight are advanced in stage and that the patient's prematurity at birth is related to the development of hepatoblastomas with unfavorable biological behavior; these findings have been published in a separate paper.[12] In this paper we report the results of the analysis of prenatal and postnatal histories of the patients including their family histories and reveal perinatal events common to hepatoblastomas in children of very low birthweight.

Methods

A total of 15 hepatoblastoma patients of very low birthweight (< 1500 g) diagnosed during the 11 years between 1985 and 1995 were identified from the data in the Japan Children's Cancer Registry and the database of medical journals which collected manuscripts written in Japanese and published in the same period.[12] Medical information on the patients was obtained from the hospitals where neonatal intensive care was given as well as from those responsible for treatment of the tumor.

The patients, nine boys and six girls, were diagnosed at the age of 6–77 months (median 16 months). Their birthweight ranged from 560 to 1380 g (median 826 g) and the gestational age was 23–33 weeks (median 25 weeks). The tumor was stage II in four patients, stage IIIA in six, stage IIIB in three and stage IV in two according to the classification of the Japanese Society of Pediatric Surgeons which was based on the number of liver segments involved, the extent of local (capsular and vascular) invasion, the regional lymph node involvement and the presence of distant metastasis.[12,13] The medical records of all patients were reviewed and the data analyzed in this study included the parents' occupation and medical history, maternal reproductive history and the patient's prenatal history. In addition to congenital abnormalities and early postnatal illnesses of the patients, treatments, medications and radiological examinations which were given while in a neonatal intensive care unit were examined. As the gestational age of the patients with a stage IIIB or IV tumor was significantly lower than that of the patients with a stage II or IIIA tumor, birth prevalence rates of congenital abnormalities, incidences of early postnatal illnesses, lengths of treatments or medications and numbers of radiological examinations in these two groups were compared.

One patient (case 1) was excluded from the statistical analysis because of insufficient information on the perinatal period. All data are presented as the range and the median. Statistical analysis was done using the Fisher's exact probability test to compare the birth prevalence rates of congenital abnormalities and the incidences of early postnatal illness. Differences between the patients with a stage II or IIIA tumor and those with a stage IIIB or IV tumor in lengths of treatments and medications and numbers of radiological examinations were evaluated by the Mann–Whitney *U*-test. Significance was defined as $P < 0.05$.

Results

Family history and prenatal and postnatal histories of the 15 hepatoblastoma patients are summarized in Tables 1 and 2.

Parents' occupation, medical history and maternal reproductive history

The occupational history was obtained from 12 fathers and 14 mothers. As far as we can tell from the information, there were no specific exposures to the reported risk factors for hepatoblastoma in the parents. Among those whose information was obtained, only one mother was positive for serum anti-hepatitis C virus (HCV) antibody, but there were no parents who were positive for serum hepatitis B antigen or who had received blood transfusion. None had a history of liver disease or familial adenomatous polyposis.

Twelve of 15 mothers had had an earlier pregnancy before they gave birth to the patient and the numbers of previous pregnancies were one in seven mothers, two in four and three in one mother. Nine mothers were parous; eight of them were unipara and one was bipara. Three mothers had a history of spontaneous abortion and another two had undergone therapeutic abortion. There was no stillbirth in the previous pregnancies.

Table 1 Family history and prenatal history of 15 hepatoblastomas in children of very low birthweight (< 1500 g)

Patient	Gestational age (weeks)	Birth-weight (g)	Gender	Parents' occupational and medical history	Reproductive history: Gravida/parity	Reproductive history: Contraceptive	Reproductive history: Treatment for sterility	During pregnancy: Alcohol	During pregnancy: Cigarettes	Complications of pregnancy: Pre-eclampsia	Complications of pregnancy: PROM	Complications of pregnancy: Infection	Intra-uterine growth retardation	Cortico-steroids	Asphy-xia	Mode of delivery	Maternal age at delivery (years)
1	33	1380	M	–	2/ND	–	ND	–	–	–	ND	–	+	–	ND	ND	30
2	24	822	M	–	0/0	–	–	–	–	–	+	+	–	ND	+	C	39
3	30	974	F	–	1/1	–	–	–	–	–	–	+	+	–	–	C	26
4	28	677	M	–	0/0	–	–	ND	ND	+	–	–	+	–	+	C	23
5	25	607	M	–	1/0	–	–	–	–	–	+	–	+	–	+	V	36
6	25	838	F	–	2/2	–	–	–	–	–	–	–	–	–	+	C	30
7	27	1160	M	–	1/1	–	–	–	–	–	–	–	–	–	ND	V	23
8	23	560	F	–	1/1	–	–	–	–	–	–	–	–	–	–	V	38
9	24	826	F	–	0/0	–	–	–	–	–	–	–	–	–	–	V	25
10	32	1188	F	–	2/1	+	+	+	–	–	+	–	+	–	–	C	37
11	25	865	F	–	3/1	–	–	–	–	–	–	+	–	–	ND	C	36
12	32	792	M	–	1/1	–	–	–	+	–	–	–	+	–	+	C	30
13	27	952	M	–	2/1	–	–	–	–	–	–	–	–	–	ND	V	26
14	23	670	M	–	1/1	–	–	–	–	–	+	+	–	–	–	V	30
15	25	734	M	HCV*	1/0	–	–	–	–	–	–	–	–	–	+	V	27

PROM, premature rupture of membrane; ND, not described; C, cesarean section; V, vaginal delivery. *HCV, hepatitis C virus carrier mother.

Table 2 Postnatal history of 15 hepatoblastomas in children of very low birthweight (< 1500 g)

Patient	Congenital abnormality	Early neonatal illnesses: Serum IgM at birth (> 20 mg/dL)	RDS	PDA	CLD	Infectious disease	GPT (> 100 IU/L)	Hepato-biliary disease	Treatment (days): Oxygen	Assisted ventilation	Photo-therapy	Blood transfusion	Blood derivatives	Medication (days): Furose-mide	Amino-phylline	Spirono-lactone	Radiological examination (*n*): Plain radiograph	CT
1	–	NE	ND	ND	ND	ND	–	–	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
2	–	+	–	–	+	+	–	–	213	155	3	+	+	300	0	0	55	1
3	–	+	–	–	–	–	–	–	13	1	3	+	+	27	27	0	4	1
4	–	NE	+	–	–	+	–	–	90	29	9	+	+	35	30	0	28	1
5	–	–	+	+	+	+	–	–	118	98	8	+	+	180	84	180	54	1
6	Atresia of EAC	NE	+	–	+	+	–	–	116	113	19	+	+	33	30	11	14	0
7	–	–	+	+	+	+	–	–	78	50	4	+	+	57	42	47	58	1
8	–	NE	–	–	–	+	–	–	112	112	0	–	+	35	0	35	26	1
9	–	–	–	+	+	+	–	–	290	166	12	+	+	385	66	352	58	2
10	–	NE	–	–	–	–	–	–	0	0	2	+	–	0	0	0	2	0
11	–	NE	+	–	–	+	–	–	28	6	3	+	+	6	118	0	7	1
12	VSD	–	–	–	–	+	–	Chole-lithiasis	4	0	27	–	+	162	17	158	20	0
13	–	–	–	–	–	+	–	–	80	0	8	+	+	88	2	58	6	0
14	–	–	–	–	+	+	+	CMV hepatitis	508	295	3	+	+	460	0	0	122	1
15	–	+	+	–	+	+	–	–	364	21	6	+	–	90	8	83	26	1

RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; CLD, chronic lung disease; GPT, glutamic–pyruvic transaminase; CT, computed tomography; NE, not examined; ND, not described; EAC, external auditory canal; VSD, ventricular septal defect; CMV, cytomegalovirus. IgM, immunoglobulin M.

Prenatal history of hepatoblastoma patients

One patient was born to a mother who had taken a contraceptive for 4 months until 6 months before she became pregnant with the patient as a result of *in vitro* fertilization. No others had taken contraceptives or had been treated for sterility. During the pregnancy of the patient one mother consumed a negligible amount of alcohol and another smoked cigarettes until 28 weeks of gestation. Pregnancy was complicated with pre-eclampsia in one mother who was treated with methyldopa and hydralazine hydrochloride to control blood pressure. Deliveries of four patients were complicated with prolonged rupture of the membrane (> 24 h). Tocolytic agents, such as ritodrine hydrochloride and magnesium sulfate, were administered in two cases. Carbazochrome sodium sulfate and tranexamic acid were used to control antepartum hemorrhage in one. Infections were suspected during the pregnancies of four patients and antibiotics such as latamoxef sodium and erythromycin were given in one case. Intrauterine growth was retarded in six patients, but no antenatal corticosteroid therapy to stimulate fetal lung maturation was given. Seven patients were delivered by cesarean section and the other seven vaginally. The mother's age when she gave birth to the patient was 23–39 years old (median 30 years old).

Congenital abnormalities and early postnatal illnesses

A small ventricular septal defect that closed spontaneously in late infancy and an atresia of the external auditory canal were congenital abnormalities seen in the patients. No other signs of congenital abnormalities, including those such as Beckwith-Wiedemann syndrome, hemihypertrophy or trisomy 18 syndrome, were seen. The serum immunoglobulin M level at birth was examined in nine patients and was higher than the upper limit of the normal range, 20 mg/dL, in three patients, suggesting the presence of intrauterine infections. Six patients suffered from respiratory distress syndrome. Symptomatic patent ductus arteriosus was diagnosed in three patients and chronic lung disease developed in seven. A variety of infections were diagnosed in 12 patients and these included bacterial and viral pneumonia, bacterial and fungal sepsis, bacterial omphalitis and cytomegalovirus hepatitis. Liver dysfunction, defined as that with high serum glutamic–pyruvic transaminase (GPT) levels (> 100 IU/L) was seen in one patient with cytomegalovirus hepatitis in whom the maximum GPT level was 757 IU/L. No other abnormality in the hepatobiliary system, except cholelithiasis in one patient, was seen. There was no significant difference between nine patients with a stage II or IIIA tumor and five patients with a stage IIIB or IV tumor in the number of congenital abnormalities or early postnatal illnesses (Table 3).

Treatments, medication and radiological examinations during neonatal intensive care

The length and frequency of treatments, length and frequency of medication and number of radiological examinations during neonatal intensive care in 14 patients, excluding case 1, are listed in Table 4. Oxygen therapy was given to 13 patients for a period of 4–508 days (median 112 days). Eleven of them were treated with assisted ventilation for 1–295 days (median 98 days). Phototherapy was necessary to control hyperbilirubinemia in 13 patients for 2–27 days (median 6 days). Twelve patients received blood transfusions and blood derivatives, such as immunoglobulins, serum albumin, plasma protein fractions, anti-thrombin III and anti-hemophilic factor XIII,

Table 3 Congenital abnormalities and early postnatal illnesses

Congenital abnormality and early postnatal illness	Stage of tumor†	
	II, IIIA ($n = 9$)	IIIB, IV ($n = 5$)
Gestational age (weeks)*	25–32 (28)	23–25 (24)
Birthweight (g)*	607–1188 (865)	560–826 (734)
Congenital abnormalities	2	0
High serum IgM at birth (> 20 mg/dL)	1	2
Respiratory distress syndrome	5	1
Symptomatic patent ductus arteriosus	2	1
Chronic lung disease	3	4
Infection	7	5
Bacterial	4	5
Viral	0	3
Fungal	1	2
Unknown	3	1
Liver dysfunction (GPT > 100 IU/L)	0	1
Cholelithiasis	1	0

*Data are expressed as the range and the median. Case 1 was excluded from the analysis because of insufficient information. IgM, immunoglobulin M; GPT, glutamic–pyruvic transaminase.

文献 6)　Maruyama K., et al. : Pediatrics International, Vol.41, P82-89, (1999).

Table 4 Length (frequency) of treatments and medication and number of radiological examinations at the neonatal intensive care unit

	No. patients*	Range	Median
Treatments (days)			
Oxygen therapy	13	4–508	112
Assisted ventilation	11	1–295	98
Phototherapy	13	2–27	6
Blood transfusion*	12	1–44	6
Blood derivatives*	12	1–15	3
Medication (days)			
Furosemide	13	6–460	88
Aminophylline	10	2–118	30
Spironolactone	8	11–352	71
Dopamine	6	5–95	34
Alphacalcidol	6	13–40	53
Ampicillin	6	2–19	4
Cefmetazole	5	3–41	4
Dexamethasone	4	11–15	12
Phenobarbital	4	18–90	40
Dobutamine	4	10–79	43
Mefenamic acid*	4	2–3	3
Lung surfactant*	4	1	1
Radiological examinations (no.)			
Plain chest or abdominal X-ray	14	2–122	26
Computed tomography	10	1–2	1

*Case 1 was excluded from the analysis because of insufficient information. †These are expressed as frequencies (times) instead of lengths (days).

Table 5 Differences in length (frequency) of treatments and medications and number of radiological examinations according to patient's stage of tumor

	Stages II, IIIA ($n = 9$)	Stages IIIB, IV ($n = 5$)	P
Treatments (days)			
Oxygen therapy	0–118 (78)	112–508 (290)	0.0040
Assisted ventilation	0–113 (18)	21–295 (155)	0.0190
Phototherapy	2–27 (8)	0–12 (3)	0.3636
Blood transfusion*	0–10 (4)	0–44 (7)	0.4376
Blood derivatives*	0–5 (2)	0–15 (2)	1.0000
Medication (days)			
Furosemide	0–180 (35)	35–460 (300)	0.0420
Aminophylline	0–118 (30)	0–66 (0)	0.1469
Spironolactone	0–180 (11)	0–352 (35)	0.7972
Dopamine	0–32 (0)	0–95 (35)	0.1898
Alphacalcidol	0–120 (0)	0–172 (0)	1.0000
Ampicillin	0–19 (0)	0–12 (0)	1.0000
Cefmetazole	0–6 (0)	0–41 (3)	0.2977
Dexamethasone	0–12 (0)	0–15 (0)	0.6064
Phenobarbital	0 (0)	0–90 (21)	0.0190
Dobutamine	0–10 (0)	0–79 (35)	0.1119
Mefenamic acid*	0–3 (0)	0–3 (0)	0.6742
Lung surfactant*	0–1 (0)	0–1 (0)	0.9255
Radiological examinations (no.)			
Plain chest or abdominal X-ray	2–58 (20)	26–122 (55)	0.0599
Computed tomography	0–1 (1)	0–2 (1)	0.3636

Case 1 was excluded from the analysis because of insufficient information. *These are expressed as frequencies (times) instead of lengths (days). Data are expressed as the range. Figures in parentheses are the median value.

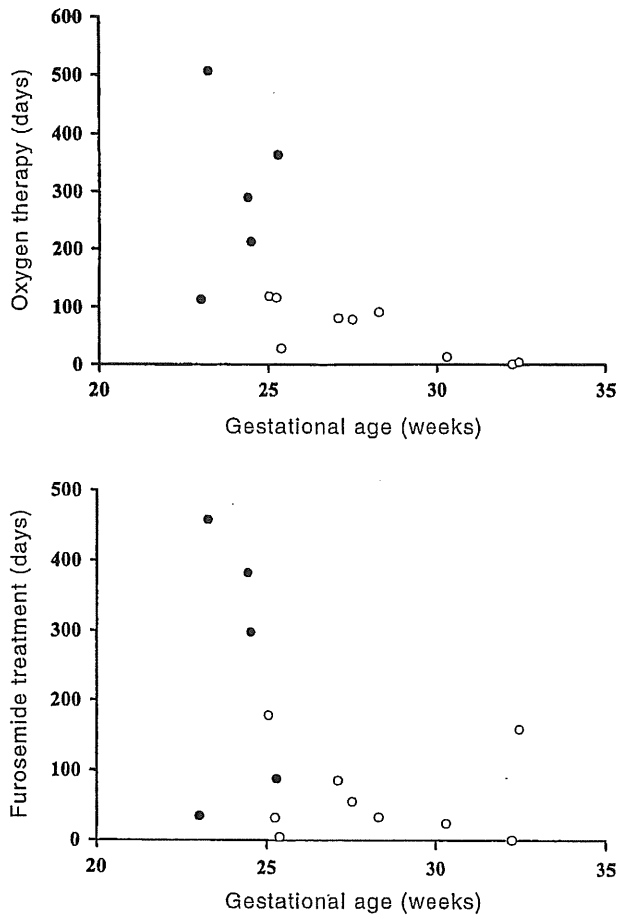

Fig. 1 Among the patients at 23–25 weeks of gestations, oxygen therapy (a) and furosemide treatment (b) tended to be longer in patients with a stage IIIB or IV tumor (●) than those with a stage II or IIIA tumor (○).

were also administered to 12 patients. Thus, all the 14 patients had received blood products or preparations derived from blood. With regard to medications, a total of 58 drugs were used during the neonatal intensive care of the patients and 12 drugs were given to four or more patients. In particular, furosemide was used in 13 patients for a period of 6–460 days (median 88 days). Aminophylline was given to 10 patients and spironolactone to eight. Plain films of the chest and the abdomen were taken in all patients and the number of radiographs was 2–122 (median 26). Examination of the brain or the abdomen by computed tomography (CT) was performed once or twice (median 1) in 10 patients.

Table 5 shows the quantitative differences between nine patients with a stage II or IIIA tumor and five patients with a stage IIIB or IV tumor in treatments, medications and radiological examinations. Lengths of oxygen therapy and assisted ventilation were significantly longer in patients with a stage IIIB or IV tumor than those with a stage II or IIIA tumor ($P = 0.0040$ and 0.0190, respectively). The furosemide treatment was also significantly longer in patients in the former group than in the latter ($P = 0.0420$). Among the patients at 23–25 weeks gestation, these treatments tended to be longer in patients with a stage IIIB or IV tumor than those with a stage II or IIIA tumor (Fig. 1). The phenobarbital treatment was longer in patients with a stage IIIB or IV tumor, as all the four patients who received phenobarbital were among the patients in this group. Although more radiographs were taken in patients with advanced tumor, the difference was not statistically significant ($P = 0.0599$).

Discussion

There were several epidemiological studies which reported relationships between high birthweight and an increased risk of specific childhood malignancies.[14,15] Our previous study was of particular importance because it revealed an association between very low birthweight (< 1500 g) and hepatoblastoma and urged determination of a hidden etiology of tumor development. The primary purpose of the present study was to reveal the family history or perinatal factors which were common to hepatoblastomas in children of very low birthweight. With respect to the parents' history and the maternal reproductive history, there was no characteristic feature. The parents were not exposed to any reported occupational risk factors. Hepatitis-causing viral infections or liver disease were not common, although one mother was positive for the antibody to the HCV. This virus is causally associated with hepatocellular carcinoma in adults, but it appears to be unrelated to childhood hepatoblastoma.[16] No patient was a member of a family with adenomatous polyposis.

One patient was born to a mother who had taken a contraceptive before she became pregnant with the patient as a result of *in vitro* fertilization. As we were unable to obtain information from each patient's family in the present study, the contraceptive was not identified and details of the treatment for infertility were not known. It is possible, as has been suggested in some case reports,[6,8] that the contraceptive or hormonal treatment accompanying *in vitro* fertilization was related to hepatoblastoma development in the child. However, the contraceptive or hormonal treatment would not make a great contribution to the association between hepatoblastoma and very low birthweight, as only one patient had a mother with this history. Other prenatal histories seemed to be etiologically insignificant and the age at which the mothers gave birth to the patients also was not significant. In the present study, the reasons for premature birth as well as those for cesarean section were not examined, but antepartum infection, intrauterine growth retardation and fetal asphyxia were supposed to be the reasons.

文献 6)　Maruyama K., et al. : Pediatrics International, Vol.41, P82-89, (1999).

In this series, six patients suffered from respiratory distress syndrome and the disease was a radiologically severe form in five patients. Symptomatic patent ductus arteriosus manifested in three patients and chronic lung disease developed in seven. Consequently at least one of the three diseases, which are frequently seen in premature infants, was diagnosed in five of the nine patients with a stage II or IIIA tumor and four of the five patients with a stage IIIB or IV tumor. Incidences of liver disease and liver dysfunction were not high in these patients, but hepatitis was caused by cytomegalovirus infection in one patient and the postnatal course was complicated with cholelithiasis from as early as 6 weeks of age in another.

The second purpose of the study was to compare the family history or perinatal factors of the patients with an advanced or unresectable tumor and those with a localized one. Our surgical and pathologic review revealed that hepatoblastomas associated with very low birthweight were at an advanced stage and that stage IIIB tumor involving all liver segments and stage IV tumor with distant metastasis developed in children with extreme prematurity at birth.[12] The gestational age and the birthweight of the patients with a stage IIIB or IV tumor were significantly lower than those of patients with a stage II or IIIA tumor.[12] These results led us to examine the differences between the characteristics of the patients. Of the treatments and medications given at a neonatal intensive care unit, oxygen therapy and assisted ventilation were continued for a longer period in stages IIIB and IV patients than stages II and IIIA patients. The length of furosemide treatment was also significantly longer in patients in the former group. More radiographs were taken in patients with advanced tumors, but the difference was not statistically significant. Diuretics, as well as oxygen and assisted ventilation, were indicated because of respiratory distress syndrome, patent ductus arteriosus and chronic lung disease. Infection of the respiratory system was another reason for the oxygen management. This information indicates that the advanced stages of the tumor are related to the longer treatments with oxygen, assisted ventilation and furosemide. As the patients with advanced tumors were extremely premature at birth, it is reasonable that these patients needed more intensive treatment; however, the advanced stages of the tumor still tended to be related to the longer treatments when only patients of extreme prematurity, 23–25 weeks gestation, were compared. Therefore, along with the results of the surgical and pathological review, it appears that there is a close correlation between the patient's prematurity, the intensive treatment due to illnesses characteristic of prematurity and the development of advanced hepatoblastoma with unfavorable biological behavior.

The relationship may be explained by assuming the presence of genes responsible for both the patient's prematurity and the development of hepatoblastoma. However, congenital anomalies seen in the patients, ventricular septal defect and atresia of the external auditory canal are not suggestive of genetic predisposition to prematurity and hepatoblastoma. Even if such genes are present, it is unlikely that they, at the same time, regulate the ability of tumor cells to invade or metastasize and decide the biological behavior of the tumor. It is likely that intensive treatments given to the infants result in the development of unfavorable hepatoblastoma. If the sensitivity to genetic damage, similar to that demonstrated in fetal monkey,[17] exists and differs according to the stage of organogenesis, the liver cells exposed to etiological factors in the earlier stage of organogenesis may transform into cells with biologically more unfavorable characteristics. It is also possible that the liver cells which are exposed to a larger quantity of carcinogens transform into more unfavorable tumor cells. There is some evidence of an association between tumor development and reactive oxygen, furosemide and spironolactone administration.[18–20] Aminophylline is known to increase mutagenesis by carcinogens.[21]

Based on the results of this study, we conclude that a case-control study should be conducted to seek the possible presence of etiologies. Although the exact etiology is not yet known, children weighing less than 1500 g at birth who are at high risk of developing hepatoblastoma should be closely monitored even after they are discharged from the neonatal intensive care unit.

Acknowledgements

We thank Shigenobu Aoki of the Faculty of Social and Information Studies, Gunma University, and Masako Tanimura, Department of Child Ecology, National Children's Medical Research Center, for their helpful comments during the statistical analysis of the data and the preparation of this manuscript.

Investigators who cooperatively contributed to the study are Naomi Ohnuma, Department of Pediatric Surgery, Chiba University School of Medicine, Chiba; Ikuo Konnai and Yutaro Matsumoto, Divisions of Neonatology and Pediatric Surgery, Iwaki-Kyoritsu General Hospital, Fukushima; Hidetoshi Suda, Department of Neonatology, Morioka Red Cross Hospital, Iwate; Tsugumi Uchiyama, Division of Surgery, Iwate Clinic Mizusawa, Iwate; Hiroshi Nishida and Chisako Mitsuishi, Maternal and Perinatal Center, Tokyo Women's Medical College, Tokyo; Toshiro Honna, Department of Surgery, National Children's Hospital, Tokyo; Yoshiteru Ohsone, Department of Neonatology, Kimitsu Chuo Hospital, Chiba; Masaki Takayanagi and Takao Etoh, Departments of Pediatrics and Surgery, Chiba Children's Hospital, Chiba; Ayumi Seki and Kiyoshi Kishi, Departments of Pediatrics and Surgery, Tottori Prefectural Central Hospital, Tottori; Makoto Mikawa, Department of Pediatrics, Kitami Red Cross

Hospital, Hokkaido; Fumiaki Sasaki, First Department of Surgery, Hokkaido University School of Medicine, Sapporo; Yoshitaka Momose, First Department of Surgery, Shinshu University School of Medicine, Nagano; Seiji Mizuno, Department of Pediatrics, Toyota Memorial Hospital, Aichi; Keizo Horibe, Department of Pediatrics, Nagoya University School of Medicine, Nagoya; Koichiro China and Hiromitsu Aoki, Department of Pediatrics and First Department of Surgery, Ryukyu University School of Medicine, Okinawa; Masanori Fujimura and Asako Koike, Department of Neonatology, Osaka Medical Center for Maternal and Child Health, Osaka; Norio Hanzawa, Department of Pediatrics, Saiseikai Yokohama City Nanbu Hospital, Yokohama; and Haruyuki Sekiguchi, Department of Pediatrics, Yokohama City University School of Medicine, Yokohama, Japan.

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