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WEIGHT LOSS AS A FACTOR IN THE DEVELOPMENT OF KERNICTERUS*

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Running head: Weight Loss and Kernicterus

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ABSTRACT

Plioplys AV, Kleinberg F, Okazaki H: Weight loss as
factor in the development of kernicterus.

Autopsy data on all newborns who died betw
1974 and 1980, inclusive, were reviewed. From the 2
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was significantly associated with the occurrence of
($P = 0.011$). The association of weight loss with
ment of kernicterus has not been reported previousl

Material and Methods

The autopsy data on all newborns who died between Jan. 1, 1974, and Dec. 31, 1980, were reviewed. During this period, 230 complete autopsies were performed on infants younger than 25 days of age, all but 19 of whom had been hospitalized in a neonatal intensive care unit. During these 7 years, there were 1,791 admissions to the unit and 233 deaths; 211 of the 233 infants were younger than 25 days of age. From the neuropathologic data on these 211, 26 cases of kernicteric staining of the brain were identified. In each case, the brain was fixed in 10% formalin solution and dissected in 7 to 10 days by coronal sectioning. The stained areas were noted, and photographs and microscopic slides were made of selected cases. The criterion for the diagnosis of kernicterus was the presence of grossly visible discoloration of the gray or white matter (or both) of the brain, consistent with the criterion used by Haymaker and associates.[12]

A control group was retrospectively chosen from the nonkernicteric infants and matched on a one-to-one basis. The groups were matched for gestational age, duration of life, and, when possible, year of birth. No attempt was made to control for sex. It was necessary to control for the duration of life because of the appreciable discrepancy between the kernicteric and the nonkernicteric infants. Only 1 of the 26 kernicteric infants died at the age of 1 day, whereas 101 of the 204 nonkernicteric infants (50%) died during the first day.

The chemistry determinations were performed in the clinical chemistry laboratories of the Mayo Clinic. The bilirubin levels were determined by a modified Evelyn Malloy method, serum sodium was determined by flame photometry, and plasma glucose was measured by a Beckman glucose analyzer with use of glucose oxidase as a substrate. The P_{O_2}, P_{CO_2}, and pH were determined on arterial blood samples by using a blood-gas analyzer (International Laboratories model 813). The hematocrit values were determined both by Coulter counter and by bedside centrifugation.

All of the charts were reviewed, and the clinical and laboratory data were abstracted. From the accumulated blood-gas determinations, the highest and lowest P_{O_2}, P_{CO_2}, and pH values were recorded and used as approximate indicators for degrees of hypoxia and acidosis.

Data were analyzed both as paired and as independent samples. Paired and two-sample *t* tests were used. In addition, the chi-square test of association and McNemar's test for correlated proportions were used. Only two-tailed *P* values are reported. Linear regression and correlation were used as well.

Results

The yearly frequency of kernicterus did not appreciably change during the study period. The overall percentage frequency was 11%.

Between the two groups, no significant difference was detected in maternal age (23.4 ± 5.9 years [mean ± SD]

for the control group and 25.2 ± 6.5 years for the kernicteric group), maternal gravidity, multiple deliveries, or premature rupture of membranes (24 hours or more before delivery). Furthermore, no significant difference was detected in the frequency of maternal illnesses, in general, during pregnancy or, in particular, in the frequency of diabetes mellitus, urinary tract infections, eclampsia, and preeclampsia.

Birth weight, gestational age, and Apgar scores at 1 and at 5 minutes did not differ significantly (Table 1). Also, no significant difference was detected between these two groups in the year of birth.

For the kernicteric infants, the duration of life ranged from 1 to 23 days (median 5.5 days). The control group was selected to match for this variable, the range being 1 to 24 days (median 5.0 days).

In the kernicteric group, 19 of 26 (73%) were male infants, whereas in the control group, 12 of 26 (46%) were male. This difference was of borderline significance when analyzed as independent samples ($P = 0.05$) as well as when analyzed by using the pairing with McNemar's test ($P = 0.052$).

The postnatal clinical factors are outlined in Table 2. There was no significant difference between the two groups in any of these clinical measurements except percentage of weight loss.

In the kernicteric infants with sepsis, the causative organisms were gram-negative rods in five cases (*Escherichia coli* in four and species not identified in one; blood cultures

were positive in four of the cases and spinal fluid in the other), group B β-hemolytic streptococcus in two (blood culture in one and endotracheal tube aspirate in the other), and *Staphylococcus epidermidis* in one (peritoneal fluid). In the control infants with sepsis, the causative organism was group B β-hemolytic streptococcus in two cases (blood culture in one case and spinal fluid in the other), *S. aureus* in one (blood culture), *E. coli* in one (blood culture), and *Pseudomonas aeruginosa* in the remaining one (endotracheal tube aspirate).

The one kernicteric infant with hemolysis had disseminated intravascular coagulation, and one control patient had Rh incompatibility.

A two-sample comparison of the means by using the *t* test revealed a significant difference (*P* = 0.022) between these two groups in the maximal percentage of weight loss in relationship to birth weight. The paired *t* test was also significant (*P* = 0.011). The maximal percentage of weight loss was calculated by using the lowest recorded weight as compared with the birth weight--all of the infants having weight determinations at least once daily. Those infants who did not have a weight loss in relationship to birth weight were ascribed a percentage loss of 0. This value ranged from 0 to 23 (mean, 12.8 ± 6.8) in the kernicteric group and from 0 to 21 (mean, 8.3 ± 6.4) in the control group. These data are presented as a scatter diagram in Figure 1. The day on which the maximal weight loss occurred did not differ between the two groups. There was no significant

difference in the percentage of weight loss by year. In infants with a birth weight of less than 2,500 g, there was no correlation between these two variables within either group (Fig. 2). The four infants with a birth weight of more than 2,500 g did have a lower percentage of weight loss.

The types of fluids and feedings that were administered to the two groups did not differ significantly (Table 3).

The use of furosemide, phenobarbital, sodium bicarbonate, and albumin was not found to differ significantly in the two groups. In both groups, the main antibiotics used were ampicillin, oxacillin, penicillin, and gentamicin, no significant difference existing between the use of these and other antibiotics.

In Table 4, the laboratory findings in both groups are shown. Hypoglycemia was defined as a plasma glucose level of less than 30 mg/dl, and hypernatremia was defined as a serum sodium concentration of more than 150 meq/liter. There was no significant difference between the two groups in any of the laboratory tests. There were too few determinati of serum albumin performed in both groups to make a meaningful comparison.

The peak bilirubin range was 4.3 to 17.7 mg/dl in the kernicteric group and 2.8 to 21.6 mg/dl in the control group. There was no correlation detected between the maximal percentage of weight loss and the peak serum bilirubin levels for each group considered separately (Fig. 3). Similarly,

no significant correlation could be detected between the maximal percentage of weight loss and the lowest P_{O_2} or the lowest pH determinations.

There was no significant difference between the two groups in the use of phototherapy, 21 of the kernicteric infants and 19 of the control infants receiving it. Three of the kernicteric infants received double-volume exchange transfusions (1 exchange each), as did five of the control patients (the number of exchanges performed being 2, 3, 6, 8, and 18, respectively). The criterion used for exchanges was a modified 1% method in which the exchange level was set at 1% of the infant's birth weight in grams to correspond to milligrams of bilirubin per deciliter. In the infants with a more complicated postnatal course, this level was reduced. Phototherapy was begun prophylactically on all infants who weighed less than 1,500 g, at unconjugated bilirubin levels of 12 mg/dl for infants from 1,500 to 2,000 g, and at levels of 15 mg/dl for infants greater than 2,000 g. By chi-square analysis and McNemar's test, there was no significant difference detected between the bilirubin therapy programs for the kernicteric and control groups.

Discussion

The results of our study corroborate the findings of previous investigators in that maternal, natal, and postnatal clinical and laboratory variables were noncontributory in distinguishing the kernicteric from the control group.[7,8] A higher frequency of kernicterus in male infants than in female

infants dying of erythroblastosis fetalis has been reported.[13] A borderline significant association ($\underline{P} = 0.05$) between kernicterus and the male sex has been noted in the premature infant. Although one early report suggested such an association, the relationship was not statistically significant ($\underline{P} = 0.14$).[14]

In our series, there was no detectable difference between the two groups in regard to sepsis, contrary to previous reports.[9] Two infants, one in each group, demonstrated evidence of hemolysis. Moreover, the two groups were comparable in the use of sodium bicarbonate, in contradistinction to a recent suggestion that it may be implicated in the genesis of kernicterus.[15]

When the issue of weight loss is discussed, the clinical and laboratory similarities between the kernicteric and control groups must be emphasized. Tables 1 through 4 document the comparability of these groups. There was no significant difference in the types or degrees of respiratory and central nervous system disorders. As judged by the extremes of monitored P_{O_2}, P_{CO_2}, pH, and hematocrit, as well as by the clinical respiratory difficulties, there was no significant difference in the degree of hypoxia and acidosis. All of these data, in conjunction with the virtually identical results of previous investigators in the other studied variables, make the finding of weight loss associated with the development of kernicterus particularly important.

The association of weight loss with kernicterus has not been reported in the past literature. In 1961, Hubbell and associates[16] reported on the effects of 48 hours of starvation in infants of diabetic mothers. They found an increase in the mean indirect serum bilirubin level in the starved infants as compared with those who were fed on days 2 and 3 of life (an increase of 6.3 mg/dl in the mean value at 72 hours of age). An increase in serum bilirubin was not confirmed by Peevy and associates,[17] who analyzed the percentage of weight loss in a similar infant population. In both series, kernicterus was not observed.

In this series, there was no association between the maximal percentage of weight loss and the peak serum bilirubin value in both the control and kernicteric infants. Similarly, no association was detected between weight loss and the lowest P_{O_2} or pH determinations. Additionally, there was no association between weight loss and birth weight in infants with a birth weight of less than 2,500 g.

These data suggest that weight loss is an independent variable that is associated with the development of kernicterus. Weight loss could be due to loss of fluid, bodily tissue (primarily fat), or both. The cause of the weight loss in our studied infants is not known, but probably both factors were involved. If fluid loss and hemoconcentration were to account for the development of kernicterus, there would be expected differences in bilirubin and hematocrit determinations, among other laboratory measurements, between the kernicteric

and control groups. Because these variables were specifically investigated and no differences were found, fluid loss alone would not seem to account for the association of kernicterus and weight loss.

Possibly, weight loss indicates relative starvation with associated lipolysis and increased nonesterified fatty acids in the circulation. Free fatty acids have been demonstrated to inhibit bilirubin conjugation[18] and to displace bilirubin from albumin.[19] If this is the explanation for this association, more attention to adequate nutritional balance in the ill, premature infant might be warranted. The concentrations of free fatty acids were not studied in our patients. This explanation remains conjectural.

The overlap of the data on maximal percentage of weight loss in the kernicteric and control groups (Fig. 1) precludes ascertainment of a maximal "safe" weight loss, just as determinations of serum bilirubin fail to give a definitely "safe" level. It should be noted that this was a pathologic study and that the relationship of weight loss and the incidence of neurologic sequelae from hyperbilirubinemia in surviving infants was not studied.

Acknowledgment

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Table 1.--Natal Factors

Factor	Group* Kernicteric (N = 26)	Control (N = 26)
Birth weight (g)	1,625 ± 632	1,660 ± 940
Gestational age (weeks)	31.5 ± 4.0	31.5 ± 4.3
Apgar score		
At 1 minute	5.2 ± 2.3	4.2 ± 2.6
At 5 minutes	6.8 ± 2.1	6.2 ± 2.6
Duration of life (days)	7.1 ± 5.5	7.0 ± 5.5

*Data are expressed as means ± SD. No significant differences were detected between the groups with use of either paired or unpaired analysis.

Factor	Group*	
	Kernicteric	Control
Maximal percentage of weight loss	12.8 ± 6.9 (25)	8.3 ± 6.4 (24)
Lowest temperature (°C)	36 ± 0.5	36 ± 0.5 (25)
30% O_2 for 24 hours	21	23
Use of positive-pressure respirator	22	25
Respiratory distress syndrome	21	21
Pneumothorax	12	13
Intracerebral hemorrhage	18	17
Seizures	18	15
Meningitis	3	1
Enclosed or subcutaneous hemorrhage	23	21
Sepsis	8	5
Hemolysis	1	1

*Except where noted in parentheses, the total number in each group was 26. Data are expressed as means ± SD for the first two entries and as number of patients for the rest of the entries. Only maximal percentage of weight loss was significantly different in the two groups--at $P = 0.022$ when the two-sample t test was used and at $P = 0.011$ when the paired t test was used.

Table 3.--Administration of Fluids

Fluids administered	Group*	
	Kernicteric	Control
Intravenous fluids		
Only	18	20
Plus breast milk	2	0
Plus formula	4	4
Plus formula and breast milk	1	0
Plus hyperalimentation	1	2
Total	26	26

*Data are shown as numbers of patients. No significant differences were detected between the two groups.

Table 4.--Laboratory Determinations

	Group*	
	Kernicteric	Control
Total bilirubin (mg/dl)		
Peak	10.46 ± 3.47 (25)	9.52 ± 4.05 (24)
At 24 hours of life	6.14 ± 1.62 (21)	5.44 ± 2.44 (21)
pH		
Lowest	7.03 ± 0.12 (25)	7.04 ± 0.12
Highest	7.44 ± 0.12 (25)	7.48 ± 0.11
P_{O_2} (mm Hg)		
Lowest	31.0 ± 11.3 (25)	28.7 ± 8.9
Highest	211 ± 83 (25)	197 ± 82
P_{CO_2} (mm Hg)		
Lowest	25.6 ± 7.9 (25)	24.8 ± 6.3
Highest	72.2 ± 14.4 (25)	76.4 ± 39.1
Hematocrit		
Lowest	30.3 ± 7.4 (23)	29.3 ± 8.2 (25)
Highest	48.7 ± 6.3	51.0 ± 9.7 (25)
Hypoglycemia	4	5
Hypernatremia	5	8

*Except where noted in parentheses, the total number in each group was 26. Data are expressed as means ± SD for all entries except the last two, in which the number of patients is indicated. No significant differences were detected between the two groups.

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Legends

Fig. 1. Scatter diagram of maximal percentage of weight loss for kernicteric versus control matched pairs. The solid square (at y = 12.8, x = 8.3) corresponds to the means for the two groups (N = 25 pairs). The solid line is the line of equality.

Fig. 2. Distribution of maximal percentage of weight loss versus birth weight in kernicteric infants and control infants.

Fig. 3. Distribution of maximal percentage of weight loss versus peak total serum bilirubin determinations in kernicteric infants and control infants.

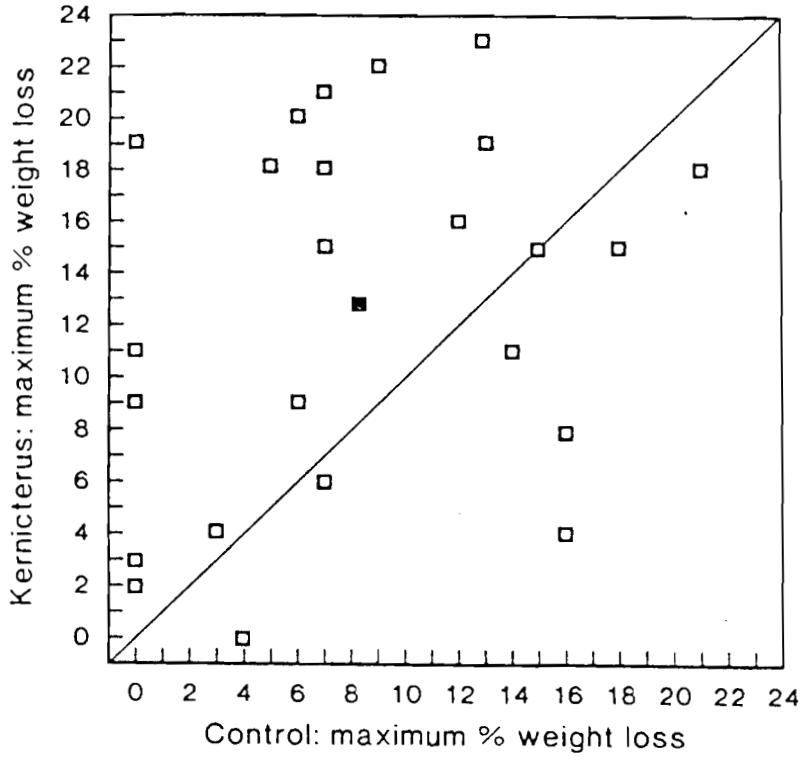
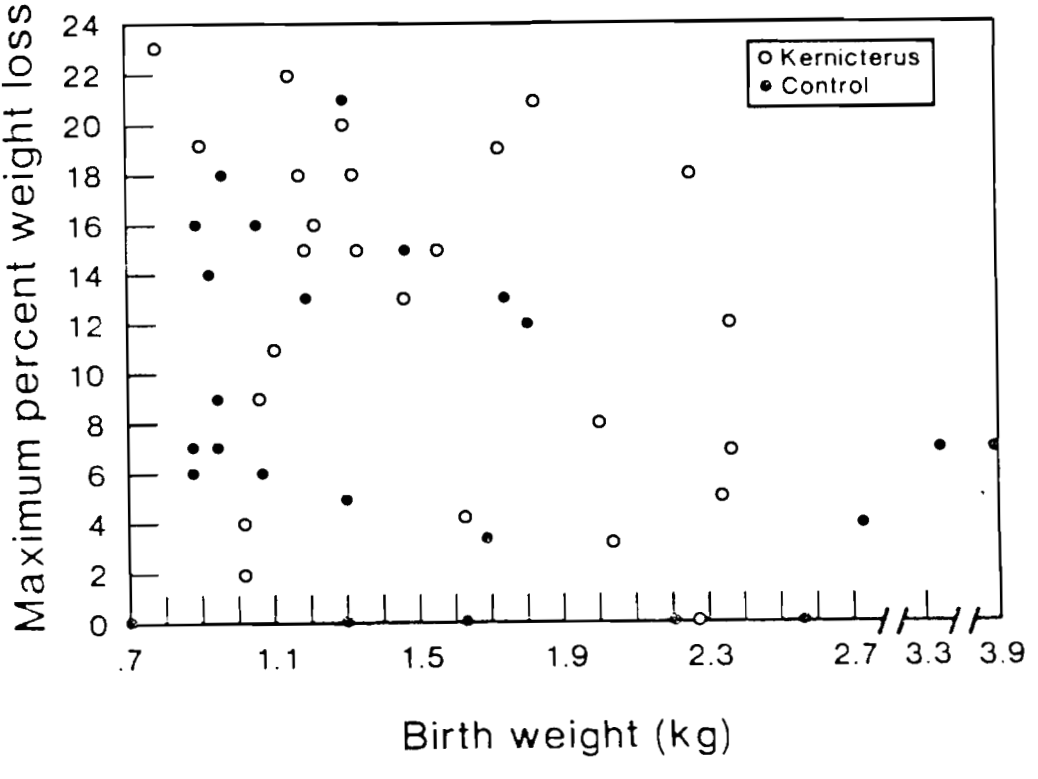
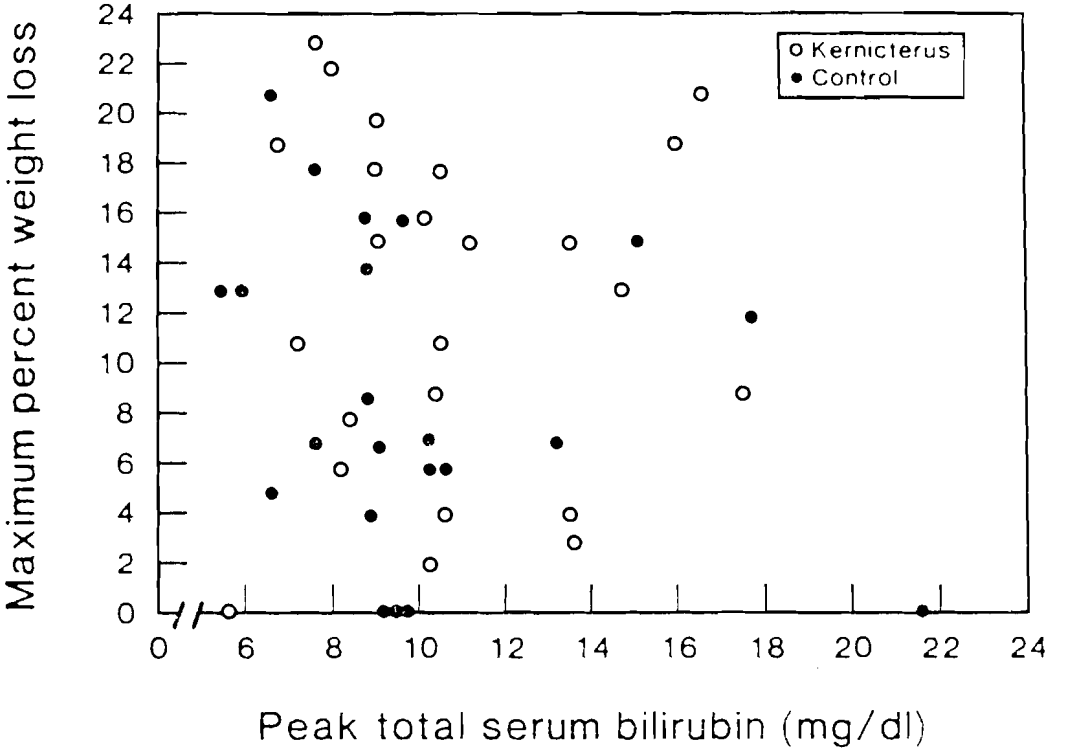

Kernicterus: maximum % weight loss
0
2
4
6
8
10
12
14
16
18
20
22
24
Control: maximum % weight loss

Fig. 1


Maximum percent weight loss
Kernicterus
Control
.7
1.1
1.5
1.9
2.3
2.7
3.3
3.9
Birth weight (kg)


Maximum percent weight loss
Peak total serum bilirubin (mg/dl)
o Kernicterus
• Control
0
2
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