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Morphologic Abnormalities in Human Infant Cerebral White Matter Related to Gestational and Postnatal Age

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Extract

The risk of selected groupings of morphologic abnormalities of infant cerebral white matter as a function of total (*i.e.*, gestational plus postnatal) age was studied in infants who had bacteria in cardiac blood aspirated at autopsy. The peak risk of hypertrophic astrocytes (HA) occurred at a younger age than the peak risk of HA and perivascular amphophilic globules (GL), which in turn occurred at a younger age than the combination of HA, GL, and necrotic foci (NF). These findings are considered compatible with the hypothesis that in infants with bacteremia, morphologic abnormalities in cerebral white matter are a function of total age.

Speculation

In infants (with or without bacteremia) morphologic abnormalities in cerebral white matter are a function of total age.

Perinatal telencephalic leucoencephalopathy (PTL) has been defined as the occurrence of both HA and GL in the cerebral white matter of infants free of diseases acknowledged as neurotoxic (13). The definition is based, in part, on the observation that HA have been shown to occur significantly more frequently with GL than would be expected if the occurrence of HA and GL were independent.

We have tried to determine whether the entity characterized by HA without GL in infant cerebral white matter (HA·$\overline{\text{GL}}$) (18) and/or the entity of GL without HA ($\overline{\text{HA}}$·GL) are early or "incomplete" manifestations of PTL (HA·GL) (14). Of the limited number of risk factors evaluated to date, postmortem bacteremia (PMB) is the only one clearly associated with HA·GL (15). The ways in which PMB may be related to PTL are presently under study. In neonatal kittens, intraperitoneal administration of an endotoxin is followed by the development of gliotic and necrotic lesions in telencephalic white matter not seen in unexposed littermates (7). No abnormalities, however, were seen in the brains of adult cats exposed to endotoxin. Thus, the relation of PMB to PTL may reflect the adverse effects of endotoxin on some maturational process unique to developing brain, such as myelinogenesis.

The results of an attempt to determine whether or not HA·$\overline{\text{GL}}$ and $\overline{\text{HA}}$·GL were also associated with PMB led us to consider the hypothesis that in infants with bacteremia, morphologic abnormalities in cerebral white matter are a function of gestational plus postnatal age.

MATERIALS AND METHODS

The sample studied consisted of all 191 infants who survived birth, died before the 4th postnatal month with systemic diseases not known to injure neonatal central nervous system, were free of gross intracranial abnormalities that could possibly injure white matter, had postmortem examinations at The Children's Hospital Medical Center of Boston between January 1, 1965 and December 31, 1967, and for whom adequate data were available.

The procedure for preparation of material for neuropathologic study is detailed elsewhere (8). The slides of all 191 infants were examined during a 6-month period in 1968 separately by each of two neuropathologists. For the first part of the study, each infant was placed into one of four mutually exclusive and exhaustive morphologic subsets: (*1*) presence of the combination of HA and GL (PTL), (*2*) presence of HA but absence of GL (HA·$\overline{\text{GL}}$), (*3*) Presence of GL but absence of HA ($\overline{\text{HA}}$·GL), and (*4*) absence of HA and GL. For the second part of this study, infants with HA and GL were subdivided into those with foci of necrosis (HA·GL·NF) and those without NF (HA·GL·$\overline{\text{NF}}$).

Autopsy records were reviewed without knowledge of white matter histology and information about selected characteristics was obtained. These characteristics were: (*1*) gestational age, (*2*) postnatal age at death, and (*3*) whether or not an organism was cultured from blood aspirated from the heart at the time of postmortem examination. An infant was considered preterm when the duration of gestation was less than 36 weeks by history (43 infants). When the duration of gestation was not known, the criteria for classifying an infant as preterm were crown-heel length of less than 45 cm (11), and histologic evidence of glomerulogenesis (8) (8 infants). Crown-heel length was used to estimate duration of gestation for calculation of total age (see below) (11).

For most evaluation procedures the sample was divided simply into younger and older halves (postnatal age at death less than 9 days, postnatal age at death equal to or greater than 9 days). "Total age" is the name we give to the sum of gestational and postnatal ages. Total age was divided into four groups: 36 weeks or less (12 infants), 37–39 weeks (9 infants), 40–42 weeks (17 infants), and greater than 42 weeks (15 infants).

Two null hypotheses were evaluated. First, PMB is not associated with HA·$\overline{\text{GL}}$, $\overline{\text{HA}}$·GL, or HA·GL in any of the four subsets of the sample classified by whether infants were born preterm or at term, and whether or not they died before the 9th postnatal day. Chi squares were calculated with Yates'

correction for continuity. Fisher's exact test was used according to the recommendations of Cochran (2). Second, in the sample with PMB, the distributions of infants with HA·$\overline{GL}$, HA·GL·$\overline{NF}$, and HA·GL·NF by total age do not differ from one another. The second hypothesis was evaluated graphically and by calculation of chi square.

RESULTS

Preterm infants who died before the 9th postnatal day comprise the only one of four groups in which the association of HA·$\overline{GL}$ with PMB achieves nominal statistical significance (Table 1).

$\overline{HA}$·GL is not associated with PMB in any of the four subsets of the population defined by gestational and postnatal age (Table 2).

In term infants who died before the 9th postnatal day, the association of HA·GL with PMB is highly significant ($P < 0.001$) (Table 3). In preterm and term infants who died on or after the 9th postnatal day, the association of HA·GL with PMB does not achieve nominal statistical significance. There appears to be no association of HA·GL with PMB in preterm infants who died before the 9th postnatal day.

In the population of infants with PMB, the peak risk of HA·$\overline{GL}$ occurs at a younger total age than the peak risk of HA·GL·$\overline{NF}$, which in turn occurs at a younger total age than HA·GL·NF, (Fig. 1). The distribution of infants with HA·$\overline{GL}$, HA·GL·$\overline{NF}$, and HA·GL·NF within the four subsets of the population classified by total age is highly unlikely to occur by chance ($\chi^2 = 20.8$, with 6 d.f. $P < 0.01$).

HA·$\overline{GL}$ and HA·GL appear to be associated with PMB in separate subsets of the population classified by gestational and postnatal age. HA·$\overline{GL}$ appears to be associated with PMB in the "youngest" subset (in terms of approximate total age), whereas HA·GL is apparently associated with PMB in an "older" subset. In none of these four subsets, however, does PMB seem to be associated with both HA·$\overline{GL}$ and HA·GL. These observations are compatible with the hypothesis that HA·$\overline{GL}$ is an early or incomplete manifestation of PTL. On the other hand, they provide no support for the hypothesis that $\overline{HA}$·GL is an early or incomplete manifestation of PTL.

DISCUSSION

The data reported here are in keeping with the broad hypothesis that whether or not an infant with bacteremia has HA·$\overline{GL}$ or HA·GL is in some way related to gestational and/or postnatal age. In what way, however, are these morphologic abnormalities a function of age? One explanation is that in certain age subsets PMB tends to occur alone, whereas in other subsets PMB tends to occur with an as yet unidentified risk factor that is associated with GL. Another explanation is that the different morphologic patterns following a single, qualitatively unique insult reflect (*1*) quantitative differences in the insult, and/or (*2*) age-dependent differences in the ability of the infant brain to respond to the insult. The latter possibility was evaluated to a greater detail because it appeared to be the most reliably and easily studied of the possibilities.

Although it is not known in our series of patients at which time in an infant's life the white matter was damaged, a limited evaluation is possible if one assumption is made. This assumption is that the insult did not occur any earlier than the last few days of gestation. This is in keeping with reports that in infants who survive birth, neonatal bacteremia tends to be acquired no earlier than the immediate perinatal period (1, 3, 10).

Preterm infants have a lag in development when compared with term infants that persists throughout most of the first postnatal year (5, 17). The amount of lag at about the 40th postnatal week is equivalent to the number of weeks before term that the infant is born (5). In addition, maturation of electroencephalographic patterns in perinates appears to be more a function of total age than of length of gestation or postnatal age alone (4, 6, 9, 16). These observations are in keeping with the idea that early development (*i.e.*, central

Table 1. *Fourfold tables of relation of postmortem bacteremia (PMB) to hypertropic astrocytes without amphophilic globules (HA·$\overline{GL}$) in four mutually exclusive and exhaustive subgroups of population classified by gestational and postnatal age dichotomies*[1]

	Preterm				Term			
	PMB (<9 days[2])		PMB (≥9 days)		PMB (<9 days)		PMB (≥9 days)	
	+	–	+	–	+	–	+	–
HA·$\overline{GL}$								
+	4	2	2	3	2	13	0	7
–	5	24	5	6	17	29	18	55
	$P = 0.03$		$P = 0.63$		$\chi^2 = 1.99$ $0.1 < P < 0.2$		$\chi^2 = 1.05$ $P \sim 0.3$	

[1] Only in preterm infants who died before the 9th postnatal day does the association of HA·$\overline{GL}$ with PMB achieve nominal statistical significance.

[2] Postnatal age.

Table 2. *Fourfold tables of the relation of postmortem bacteremia (PMB) to morphologic entity characterized by $\overline{HA}$·GL*[1]

	Preterm				Term			
	PMB (<9 days[2])		PMB (≥9 days)		PMB (9 days)		PMB (≥9 days)	
	+	–	+	–	+	–	+	–
$\overline{HA}$·GL								
+	0	2	0	1	7	8	2	6
–	9	24	7	8	12	34	16	56
	$P = 0.55$		$P = 0.56$		$\chi^2 = 2.23$ $P < 0.2$		$\chi^2 = 0$ $P \sim 0.99$	

[1] The association of $\overline{HA}$·GL with PMB does not achieve nominal statistical significance in any of the four subsets of the population.

[2] Postnatal age.

Table 3. *Fourfold tables of relation of postmortem bacteremia (PMB) to hypertropic astrocytes with amphophilic globules (HA·GL)*[1]

	Preterm				Term			
	PMB (<9 days[2])		PMB (≥9 days)		PMB (<9 days)		PMB (≥9 days)	
	+	–	+	–	+	–	+	–
HA·GL								
+	0	2	4	1	8	2	8	16
–	9	24	3	8	11	40	10	46
	$P = 0.55$		$P = 0.08$		$\chi^2 = 10.84$ $P < 0.001$		$\chi^2 = 1.51$ $0.2 < P < 0.3$	

[1] HA·GL appears to be associated with PMB in all groups except preterm infants who died before the 9th postnatal day.

[2] Postnatal age.

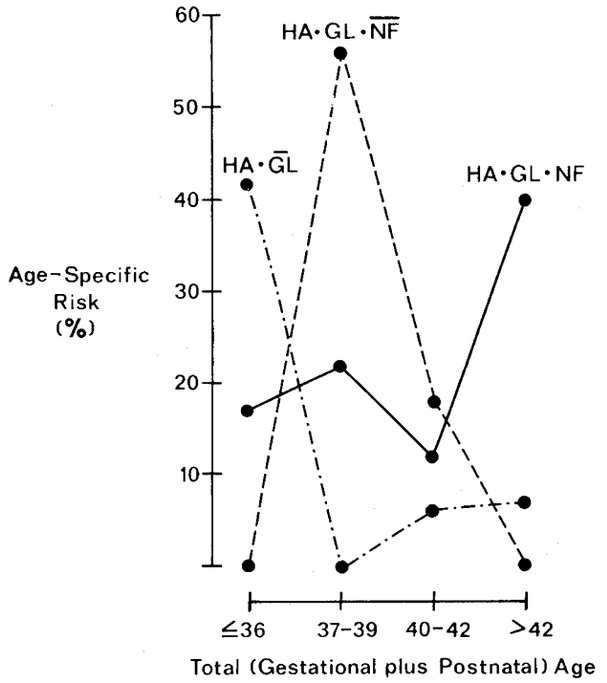

Fig. 1. In infants who had bacteria in cardiac blood aspirated at autopsy the peak risk of hypertrophic astrocytes without accompanying amphophilic globules (*HA·$\overline{GL}$*) occurred at a younger total age than the peak risk of hypertrophic astrocytes and amphophilic globules without accompanying necrotic foci (*HA·GL·$\overline{NF}$*) which in turn occurred at a younger age than the combination of hypertrophic astrocytes, amphophilic globules and necrotic foci (*HA·GL·NF*). These findings are viewed as compatible with the hypothesis that, in infants with bacteremia, morphologic abnormalities in cerebral white matter are a function of gestational plus postnatal age.

nervous system maturation) is a function of total age. The responsiveness of cells within infant cerebral white matter to an insult may also be a function of total age. Support for this comes from the observations reported here that, in infants with PMB, the pattern of white matter abnormalities appears to correlate with both gestational age (preterm or term) and postnatal age.

A total age was therefore calculated for each infant. Patterns of white matter abnormalities were then evaluated as a function of total age. The sequential progression with total age of peak risks of HA·$\overline{GL}$, HA·GL·$\overline{NF}$, and HA·GL·NF in infants with PMB is compatible with the hypothesis that the response of infant white matter to PMB is a function of gestational plus postnatal age.

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18. The absence of a characteristic is represented by a bar above it. Use of the dot means that the characteristics to the right and to the left are satisfied. HA·$\overline{GL}$ therefore refers to those infants with HA but without GL.

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