Are hypertrophic astrocytes a sufficient criterion of perinatal telencephalic leucoencephalopathy?¹

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SUMMARY To determine if the presence of amphophilic globules (GL) in infant cerebral white matter was a necessary criterion of perinatal telencephalic leucoencephalopathy (PTL), the epidemiological features of infants who had PTL—that is, hypertrophic astrocytes and amphophilic globules (HA·GL)—in their cerebral white matter were compared with those of infants who had hypertrophic astrocytes, but who did not have amphophilic globules (HA·GL). Postmortem bacteraemia was seen much more frequently in infants with HA·GL than in infants with HA·GL (P < 0.05). In addition, infants with HA·GL tended to die at older postnatal ages than infants with HA·GL. These observations are in keeping with the view that HA·GL and HA·GL are not epidemiologically identical. The operational definition of PTL therefore remains the occurrence of both HA and GL in infant cerebral white matter.

Focal necrosis of cerebral white matter in infants has been appreciated as an abnormal finding since the time of Virchow (1868). Only in recent years, however, has there been appreciation of other morphological abnormalities of infant cerebral white matter (Gilles and Murphy, 1969).

In preparation for epidemiological studies designed to evaluate potential 'causes' of these abnormalities, it was necessary to determine if each abnormality was independent of the others. This was achieved by a search for clusters (Leviton and Gilles, 1971).² Hypertrophic astrocytes (HA) and perivascular amphophilic globules (GL) occurred together much more frequently than was expected if these were independent variables. Because of this strong association of HA with GL, it was considered that their occurrence together in the cerebral white matter of infants might represent a distinct morphological entity. The name perinatal telencephalic leucoencephalopathy (PTL) was applied to this entity.

In a number of older children and adults we have seen small firm brains with a prominent reduction of cerebral white matter in all regions except the anterior temporal lobes (Gilles, Leviton, and Murphy). The clinical history of these patients and the morphology of their brains appeared compatible with predictions of the sequelae of PTL (Gilles and Murphy, 1969).

Firstly, the paucity of white matter is in keeping with the idea of interference with the process of myelinogenesis. Secondly, the fibrillary gliosis is compatible with the prior presence of HA. Thirdly, the lack of anterior temporal lobe involvement in the face of gliosis and paucity of white matter elsewhere in the cerebral hemispheres is what may be expected with an insult occurring before the time of myelinogenesis in the anterior temporal lobe—that is, before the middle of the first year.

Two hypotheses have been formulated to account for both the paucity of white matter and

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the white matter gliosis. In one of these hypotheses, an insult to myelinogenesis results in the release of substances that serve as a stimulus for the presence of HA. In the other hypothesis, an insult to myelinogenesis results in the transformation of pre-myelinated glial cells to HA. In either of these hypotheses the presumed late sequelae of PTL are adequately accounted for by the prior presence of HA. There is no need to involve the prior presence of GL. The possibility was therefore considered that HA in the cerebral white matter of young infants, with or without GL, might be an adequate criterion of PTL.

Our understanding of cerebral white matter abnormalities in infants has been facilitated by employing concepts of set theory (Leviton and Gilles, 1971). The set of HA, which consists of all infants who died with HA in their cerebral white matter, may be divided into subsets. We are concerned here with only two subsets of HA: HA·GL (HA without GL) and HA·GL (HA with GL). The entity of PTL has been operationally defined (vide infra) as the subset HA·GL. To extend the definition of PTL to the entire set of HA, the subset HA·GL should have epidemiological features virtually identical with those of the subset HA·GL. Thus, anencephaly and spina bifida have been considered 'as one causal entity rather than two' (MacMahon and Pugh, 1970), because of similarities of association with ethnic groups, socioeconomic status, sex, maternal age and parity, similarity in trends of frequency over time, and the occurrence of both anomalies in the same family (MacMahon, Pugh, and Ingalls, 1953).

If the entity HA·GL and the entity HA·GL have very similar epidemiological features, then the two may be merged to form an entity characterized by HA. This would facilitate future epidemiological studies. The following report is a comparison of the epidemiological features of HA·GL and of HA·GL.

METHODS

The base population consisted of all 191 infants who survived birth, died at Children’s Hospital Medical Center of Boston between 1 January 1965 and 31 December 1967, with a postnatal age of less than 4 months, were free of gross intracranial abnormalities associated with white matter injury, did not have diseases known to injure the central nervous system, had microscopic examination of the brain, and for whom adequate epidemiological data were available.

The procedure for preparation of material for the neuropathological study is detailed elsewhere (Gilles and Murphy, 1969). During a six month period, the slides of all 191 infants were examined separately by each of two neuropathologists who had no knowledge of the clinical history or general necropsy findings. For the purposes of this study, each infant was placed into one of three mutually exclusive and exhaustive morphological categories: (1) presence of hypertrophic astrocytes and absence of amorphophilic globules (HA·GL), (2) presence of hypertrophic astrocytes and amorphophilic globules (HA·GL), and (3) absence of hypertrophic astrocytes (HA). All statistical evaluations were limited to comparing infants with HA·GL with infants with HA·GL.

Necropsy records were reviewed without knowledge of the white matter histopathology. Anamnestic and anatomical information about potential risk factors was obtained from each necropsy record. The anamnestic information consisted of: (1) gestational age, (2) date of death, (3) postnatal age at death, (4) whether or not there was mention of cardiac catheterization, thoracic surgery, or abdominal surgery, (5) whether or not an organism was cultured from blood aspirated from the heart at the time of postmortem examination.

Those risk factors of an anatomical nature with morphological evidence of congenital heart disease, hyaline membrane disease, amniotic fluid aspiration, pneumonia, and peritonitis.

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 less than 45 cm (Gruenwald and Minh, 1960) and histological evidence of glomerulogenesis (Kissane and Smith, 1967) (eight infants).

Postnatal age at death may be an indirect measure of when an insult could have occurred, whereas total (gestational plus postnatal) age at death may be a measure of 'vulnerability' or 'responsiveness' of maturing cerebral white matter (Leviton and Gilles, 1973b). The population of infants with HA in their cerebral white matter, therefore, was classified by postnatal age. The four postnatal age groupings were those that divided the base population into approximate quarters (Leviton and Gilles, 1973a). The five total age groupings were: < 36 weeks, 37–39 weeks, 40 weeks, 41–43 weeks, and > 43 weeks.

Three null hypotheses were tested. The basic form of the first null hypothesis is that the cumulative

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frequency of deaths by age of infants with HA*GL does not differ from that of infants with HA*GL. This was tested separately for postnatal age and total (gestational plus postnatal) age. The probability of the random occurrence of the observed differences was determined by the Kolmogorov-Smirnov two-sample test (Siegel, 1956).

The second null hypothesis is: the distribution of the annual occurrence of HA*GL during the three years of this study does not differ from the annual occurrence of HA*GL. A $\chi^2$ value was obtained for the observed distribution.

The generalized form of the last null hypothesis is: in the population of infants who had HA in their cerebral white matter, the occurrence of GL is independent of each risk factor. This was tested separately for distributions by postnatal age and total age by the Mantel-Haenszel procedure (Mantel and Haenszel, 1959).

![Graph](http://jnnp.bmj.com/content/36/3/383/F3)

**FIG. 3.** The marked rise in the frequency of occurrence of HA*GL in 1967 is in sharp contrast with the almost imperceptible increase in the frequency of HA*GL. The observed distribution of all infants with HA by whether or not they had GL and by year of death, however, may represent random phenomena ($\chi^2 = 2.52, 0.2 < P < 0.3$ with 2 degrees of freedom).

**RESULTS**

Of the 191 infants in the study population 33 had HA*GL and 41 had HA*GL. Infants with HA*GL tended to die at older postnatal ages than infants with HA*GL (P > 0.05 by the Kolmogorov-Smirnov two-tailed test) (Fig. 1). On the other hand, the tendency for infants with HA*GL to die at older ages than infants with HA*GL is minimal when infants are classified by total (gestational plus postnatal) ages (Fig. 2).

The annual rate of HA*GL was not appreciably different from that of HA*GL in both 1965 and 1966 (Fig. 3). In 1967, however, the rate of HA*GL was almost double that of HA*GL. The distribution by year of death of infants with HA*GL, nevertheless, is not significantly different from that of infants with HA*GL ($\chi^2 = 2.52$ with 2 d.f., 0.2 < P < 0.3).

In infants with HA in their cerebral white matter, GL are positively associated with post-
TABLE 1
SUMMARY CHI SQUARE VALUES FOR ASSOCIATION OF GL WITH SELECTED RISK FACTORS IN INFANTS WITH HA*

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Summary $\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart disease</td>
<td>0.39</td>
</tr>
<tr>
<td>Postmortem bacteraemia</td>
<td>4.31†</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0.00</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>0.13</td>
</tr>
<tr>
<td>Amniotic aspiration</td>
<td>0.09</td>
</tr>
<tr>
<td>Hyaline membranes</td>
<td>0.02</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>0.08</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>0.11</td>
</tr>
<tr>
<td>Gestational age &lt; 36 weeks</td>
<td>5.40†</td>
</tr>
</tbody>
</table>

* The infants have been classified by postnatal ages for these determinations. GL are positively associated with postmortem bacteraemia and negatively associated with preterm birth.
† $P < 0.05$.

TABLE 2
SUMMARY CHI SQUARE VALUES FOR ASSOCIATION OF GL WITH SELECTED RISK FACTORS IN INFANTS WITH HA*

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Summary $\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart disease</td>
<td>0.34</td>
</tr>
<tr>
<td>Postmortem bacteraemia</td>
<td>4.43</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0.19</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>1.25</td>
</tr>
<tr>
<td>Amniotic aspiration</td>
<td>0.15</td>
</tr>
<tr>
<td>Hyaline membranes</td>
<td>0.01</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>0.00</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>2.69</td>
</tr>
<tr>
<td>Gestational age &lt; 36 weeks</td>
<td>0.18</td>
</tr>
</tbody>
</table>

* The infants have been classified by total (gestational plus postnatal) ages for these determinations. GL are positively associated with postmortem bacteraemia.
† $P < 0.05$.

TABLE 3
DISTRIBUTION OF INFANTS WITH HA-GL AND HA-GL BY WHETHER OR NOT THEY HAD POSTMORTEM BACTERAEMIA (PMB)*

<table>
<thead>
<tr>
<th>Postnatal age (days)</th>
<th>&lt;3</th>
<th>3-8</th>
<th>9-30</th>
<th>&gt;30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HA-GL</td>
<td>HA-GL</td>
<td>HA-GL</td>
<td>HA-GL</td>
</tr>
<tr>
<td>Postmortem bacteraemia+</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>7</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Total age (weeks)</td>
<td>&lt;36</td>
<td>36-39</td>
<td>40</td>
<td>41-43</td>
</tr>
<tr>
<td></td>
<td>HA-GL</td>
<td>HA-GL</td>
<td>HA-GL</td>
<td>HA-GL</td>
</tr>
<tr>
<td>Postmortem bacteraemia+</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
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<td></td>
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<td>7</td>
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<tr>
<td></td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

* The infants are classified by postnatal age in the top set of fourfold tables and by total (gestational plus postnatal) age in the lower set.

TABLE 4
DISTRIBUTION OF INFANTS WITH HA-GL AND HA-GL BY WHETHER OR NOT THEY HAD PRETERM BIRTH*

<table>
<thead>
<tr>
<th>Postnatal age (days)</th>
<th>&lt;3</th>
<th>3-8</th>
<th>9-30</th>
<th>&gt;30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HA-GL</td>
<td>HA-GL</td>
<td>HA-GL</td>
<td>HA-GL</td>
</tr>
<tr>
<td>Preterm birth+</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Total age (weeks)</td>
<td>&lt;36</td>
<td>37-39</td>
<td>40</td>
<td>41-43</td>
</tr>
<tr>
<td></td>
<td>HA-GL</td>
<td>HA-GL</td>
<td>HA-GL</td>
<td>HA-GL</td>
</tr>
<tr>
<td>Preterm birth+</td>
<td>4</td>
<td>7</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>9</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>6</td>
<td>9</td>
<td>5</td>
</tr>
</tbody>
</table>

* The infants are classified by postnatal age in the top set of fourfold tables and by total (gestational plus postnatal) age in the lower set.
m ortem bacteraemia regardless of whether the
infants are classified by postnatal age only or by
total age (Tables 1 to 3). The negative association
of GL with preterm birth, evident when the
infants are classified by postnatal age, is virtually
nonexistent when infants are classified by total
age (Table 4).

**DISCUSSION**

Aetiology is best considered as dealing not with
the ‘causes’ of an entity in a narrow sense of
that term, but rather with those factors that
increase the probability of that entity occurring.
It is for this reason that the present study is
concerned with ‘risk factors’.

An operational definition provides objective
criteria by which any observer can decide, for
any particular case, whether the term does or
does not apply to that case (Bridgeman, 1927).
This allows testing of the hypothesis on which
the definition is based.

The decision to broaden or narrow an opera-
tional definition should be a function of the
purpose served by definition. At present, the
goal of our studies of infant cerebral white
matter abnormalities is the recognition of risk
factors. A broadened definition of PTL could
minimize the population size necessary to
identify a risk factor—that is, it could increase
efficiency (Miettinen, 1970). On the other hand,
a broader definition could increase bias in the
estimation of the effect under study—that is, it
might reduce validity (Miettinen, 1970). Any
increase in efficiency, however, should not be at
the expense of validity.

Differences in the ability of infant cerebral
white matter to respond to an insult may be a
function of total (gestational plus post-natal) age
(Leviton and Gilles, 1973b). Evidence for this
‘total age’ concept was obtained by evaluating
the frequency of selected combinations of mor-
phological abnormalities in infants who had
postmortem bacteraemia, a risk factor clearly
associated with HA-GL (Leviton and Gilles,
1972). In that population, the risk of HA-GL
occurred at a younger total age than the peak
risk of HA-GL. In the data reported here, how-
ever, the distribution of infants with HA-GL by
total age, does not differ significantly from that
of infants with HA-GL. This lack of appreciable
difference between total age specific risks of
HA-GL and HA-GL would therefore appear to
reflect the effect not only of bacteraemia but also
of other insults. This is compatible with the
hypothesis that HA-GL and HA-GL are not
necessarily aetiologically identical. The promi-
nent difference in postnatal age distributions
between HA-GL and HA-GL does not help in
distinguishing differences in aetiology for it is
compatible with differences in the time of
occurrence of a single insult—that is, response
is a function of infant’s age—or with differences
in the time of multiple insults—that is, response
is a function of age and/or nature of insult.

The prominent increase in frequency of
HA-GL in 1967 quite closely resembled the
increased frequency of PMB in the base popula-
tion in 1967 (Leviton and Gilles, 1973a). The
difference in temporal patterns between HA-GL
and HA-GL (Fig. 3) may therefore be additional
evidence that the two subsets are not aetiologi-
cally identical. The most convincing evidence
that HA-GL and HA-GL are not epidemiologically
identical is that HA-GL is strongly associated
with postmortem bacteraemia, whereas HA-GL
is not (Tables 1 and 2). Since HA-GL and
HA-GL are not epidemiologically identical a
loss of validity may be expected if the definition
of PTL were broadened to include the entire
set of HA. The operational definition of PTL,
therefore, will not be broadened.

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