Increased brain weight/liver weight ratio as a necropsy sign of intrauterine undernutrition

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SYNOPSIS Comparison of the brain weight/liver weight ratio¹ with the body weight of 95 stillborn and neonatally deceased infants of gestation 25-42 weeks shows that in appropriately grown infants the mean value ratio is 2.8 and is unchanged with increasing maturity. The normal range is 1.7-4.1. Survival time has no significant effect on the ratio as studied in this necropsy population. Dysmature infants of body weight less than 1 SD below the mean body weight for gestation are characterized by a brain:liver weight ratio of 4.5 or more. On the basis of these observations the brain:liver weight ratio may be employed as a guide to the prenatal nutrition of infants at necropsy.

It is now widely recognized that at least one-third of all infants of low birth weight are abnormally small for gestational age and that the maturity of such infants may vary widely (Dawkins, 1965; Gruenwald, 1965). In some cases genetic factors are of importance, as in the growth retardation of the autosomal trisomy syndromes (Schutt, 1965), and occasionally prenatal infection may be responsible, but most of these 'light-for-dates' infants are so-called dysmature babies who have been subjected to intrauterine undernutrition through subnormal maternal-fetal nutrient transfer (Wigglesworth, 1966).

At necropsy, severely dysmature infants show consistent abnormalities of organ size compared with normally grown premature infants of similar weight and also with normally grown infants of the same gestational age (Gruenwald, 1963). Dysmature babies born near term are usually easy to recognize but it may be difficult to decide whether a premature infant is growth retarded, particularly if the exact gestation is in doubt. However, the ratio of brain weight to liver weight appears to be a convenient guide to the nutritional status of the individual infant since in stillborn infants born after 36 weeks' gestation the brain:liver weight ratio increases with decreasing body weight (Dawkins, 1964). In this paper an attempt is made to define the normal range of brain:liver weight ratio values for a necropsy

population of live and stillborn infants so that the ratio may be employed as an aid to the postmortem diagnosis of dysmaturity.

Material and Methods

Body weight, brain, and liver weights were taken from necropsy reports on fresh stillborn and neonatally deceased infants examined by the Edinburgh paediatric pathology service during the period 1970-71. Cases were selected in which a confident antenatal estimate of gestation had been made from the menstrual history and in which neuro-anatomical findings, particularly cerebral convolution development and myelination, were consistent with this estimate. Organ weights were available in 106 such cases of which 11 with gross disorders of brain or liver were excluded from the analysis: these were four infants with Rhesus isoimmunization and hepatomegaly, six infants with congenital hydrocephalus, and one infant with micrencephaly.

The remaining 95 cases were arranged in nine gestational age groups from 25-26 to 41-42 weeks and in each group the mean body weight and standard deviation (SD) were determined. A further grouping into three categories according to body weight was then made, group +1 having a body weight greater than 1 SD above the mean, group 0 having a body weight within 1 SD of the mean, and group -1 having a body weight less than 1 SD below the mean. The body weight of infants in group -1 was less than or only slightly greater than the 10th centile as defined by Lubchenco, Hansman,

¹The term 'brain weight/liver weight ratio' is employed as it is already in common usage, but for convenience, values are expressed throughout as quotients.

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Dressler, and Boyd (1963). The normal range of the brain:liver weight ratio was estimated using probability paper by the method of Neumann (1968).

Results

Table I lists the ratios according to gestational age and body weight and shows that in groups +1 and 0 the mean brain:liver weight ratio is close to 3.0 at all ages after 27 weeks' gestation. Values from groups +1 and 0 irrespective of gestational age may therefore be examined in a frequency distribution histogram to find the normal range of the brain:liver weight ratio. Figure 1 shows that the distribution is Gaussian in type with a mode at 2.8-2.9, although slightly skewed to the right owing to a small excess of high values. The lowest observed value is 1.7 so that if the distribution were wholly normal the highest value would be 4.0-4.1. Seven values which lie between 4.2 and 4.7 are likely to be abnormal.

These observations are supported by the probability plot (Figure 2). The plot for the total population shows that it is non-homogeneous, but taking points of truncation at 2.0 and 3.9 the plot for the reconstructed distribution follows a straight line and gives the 95% limits of the normal range as 1.7-4.0, with the mean at 2.8.

From Table I it is seen that infants of body weight group -1 and gestation 25-30 weeks have brain:liver weight ratios within the normal range of 1.7 to 4.1. In contrast, of 15 group -1 infants of

Fig. 1 Frequency distribution of brain:liver weight (BL) ratio in infants of body weight greater than 1 SD below the mean.

gestation 31-42 weeks, 11 have brain:liver weight ratios of 4.5 or higher while the remaining four infants have values in the normal range. Abnormalities of pregnancy and labour and necropsy findings in these 15 infants are summarized in Table II. In none of the 11 infants with high values were there congenital malformations or pathological findings other than chronic placental insufficiency

Gestation (weeks)	No. of Cases	Body Weight (mean $\pm$ 1 SD)	Brain Weight/Liver Weight Ratios		
			Body Weight		
			> 1 SD Above Mean	Within 1 SD of Mean	< 1 SD below Mean
25-26	4	736 $\pm$ 88	2.8	2.0, 2.1	1.8
27-28	12	1108 $\pm$ 157	2.3, 2.4	2.7 (2.3-4.3) ¹	2.5, 3.5, 3.5
29-30	5	1304 $\pm$ 232	2.7	3.5 (3.2-3.8) ¹	3.2
31-32	8	1666 $\pm$ 218	2.8	3.2 (2.5-4.3) ¹	3.1, 3.7, 5.2
33-34	8	1694 $\pm$ 410	3.1	3.1 (2.2-4.1) ¹	8.4
35-36	7	1939 $\pm$ 453	3.4	2.9 (2.3-3.5) ¹	4.5, 5.8
37-38	11	2485 $\pm$ 660	2.6, 3.0	3.4 (2.8-4.4) ¹	3.4, 4.8, 5.2
39-40	24	3013 $\pm$ 662	2.0, 2.1, 2.4, 2.7	3.3 (2.0-4.7) ¹	4.8, 5.2 5.4, 5.7
41-42	16	3290 $\pm$ 687	1.7, 2.0, 2.7	2.7 (1.7-4.1) ¹	3.1, 6.2

Table I Brain weight/liver weight ratios compared with body weight at different stages of gestation

¹Mean and range of values

Fig. 2 Probability plot. x—x total population. A, B, points of truncation. o—o reconstructed normal distribution

to account for low body weight. On the other hand, an adequate explanation other than placental insufficiency is available for the low body weight of the four infants with a normal brain:liver weight ratio, three of these infants dying from renal agenesis and the other from chronic diarrhoea and dehydration complicated terminally by cerebral water intoxication.

The influence of survival time on the brain:liver

Survival Time	No. of Cases ¹	Brain:Liver Weight Ratio	
		Range	Mean
Stillborn	14	1.7–4.4	2.75 ^a
½–24 hours	15	2.3–4.1	2.97
25–72 hours	11	2.2–4.2	3.17
73–120 hours	10	2.4–4.7	3.28 ^{a, b}
> 120 hours	10	2.0–3.8	2.76 ^a

Table III Brain weight/liver weight ratios compared with survival time

¹Infants of gestation 31–42 weeks and body weight > 1 SD below the mean.

^aP 0.10

^bP 0.10

weight ratio in infants of body weight groups +1 and 0 is analysed in Table III. The mean ratio increases gradually over the first five days of life and is 20% higher in infants aged 73–120 hours than in stillborn infants. Subsequently, the mean brain:liver weight ratio returns to the earlier level, and is the same in infants surviving for more than five days as in stillborn infants. However, there is almost complete overlap in the range of individual values of infants of different survival so that these mean differences are not statistically significant.

Discussion

At the postmortem examination of a newborn infant it is often necessary to determine whether growth retardation has occurred because prenatal

Case	Brain:Liver Weight Ratio	Gestation (weeks)	Abnormalities of Pregnancy and Labour	Maternal Urinary Oestriol Levels (mg/24hr)	Primary Necropsy Findings
1	8.4	34	Induction of labour for preeclampsia, placental infarction	3.2, 1.9	Antepartum asphyxia; stillborn
2	6.2	41	Caesarean section in elderly primigravida, smaller of twins	3.0	Pulmonary haemorrhage
3	5.8	35	Caesarean section for maternal hypertension	***	Intraventricular haemorrhage
4	5.7	40	Maternal urinary tract infection	***	Necrotizing enterocolitis
5	5.4	40	No antenatal care, placental infarction	***	Antepartum asphyxia; stillborn
6	5.2	39	Caesarean section for foetal distress and breech presentation	***	Antepartum asphyxia; liveborn
7	5.2	37	Induction of labour for preeclampsia, placental infarction	2.0	Antepartum asphyxia; stillborn
8	5.2	32	Premature labour, placental infarction	***	Antepartum asphyxia; stillborn
9	4.8	39	Preeclampsia, smaller of twins	***	Pulmonary haemorrhage
10	4.8	38	Induction of labour for arrested foetal growth	5.2, 7.8	Hyaline membrane disease
11	4.5	35	Premature labour, placental infarction	7.9, 4.1	Antepartum asphyxia; stillborn
12	3.7	32	Premature labour	***	Renal agenesis
13	3.4	37	Premature labour	***	Dehydration; cerebral water intoxication
14	3.1	41	Preeclampsia	***	Renal agenesis
15	3.1	32	Premature labour	***	Renal agenesis

Table II Clinico-pathological findings in infants of body weight < 1 SD below the mean and gestation 32–42 weeks

undernutrition is an important cause of intrapartum death, and, furthermore, the morbidity of liveborn dysmature infants is different to that of premature infants (Hutchison, 1972). The necropsy diagnosis of dysmaturity depends on the recognition of the characteristic abnormalities of organ weight and composition described by Gruenwald (1963) and Naeye (1965). Various organs are reduced in size but the liver is particularly small, while in contrast the brain remains near normal in size for gestational age. Similar organ sizes are found in experimental prenatal growth retardation in the sheep (Wallace, 1945), the rat (Wigglesworth, 1964), and the Rhesus monkey (Myers, Hill, Holt, Scott, Mellits, and Cheek, 1971). However, in necropsy practice, comparison of organ weights with tables is inconvenient and may not always be helpful in deciding whether an individual infant is growth retarded owing to the wide range of normal values at all stages of development.

The present study confirms Dawkins' (1964) observation that the mean brain:liver weight ratio in average weight infants is close to 3.0 and shows that this is true both of stillborn infants and of neonatally deceased liveborn infants irrespective of gestational age. The range of values for optimally nourished infants (group +1) is 1.7-3.4 but the normal range for the population as a whole as given by the frequency distribution and the probability plot is surprisingly wide at 1.7-4.1. This is unlikely to be because the sample analysed was insufficiently large since the SD for the body weights at each gestational age group correspond closely to Gruenwald's necropsy series (1963). Seven infants in body weight group 0 gave abnormal brain:liver weight ratio values in the range 4.2-4.7. However, an excess of high values might be expected in body weight group 0. Some less severely undernourished infants will tend to have a body weight which remains within 1 SD of the mean although having a high brain:liver weight ratio, since the liver weight is generally reduced to a greater extent than the body weight in dysmaturity (Gruenwald, 1963). Furthermore, some undernourished infants who would have been in body weight group +1 if optimally nourished will fall into group 0.

In comparison with this estimate of the normal range, a high brain:liver weight ratio was obtained in 11 infants of low body weight (group -1) and gestation 31 weeks or more, in each case the value being in excess of 4.4. In seven of the cases in this group pregnancy was complicated by preeclampsia, hypertension, twin birth, or low urinary oestriol excretion, and of the remaining cases two were stillborn infants with massive chronic placental infarction. A brain:liver weight ratio greater than

4.4 therefore appears to be characteristic of clinical dysmaturity. Only one infant in body weight group 0 had a brain:liver weight ratio greater than 4.4, and for reasons outlined above this infant also may have been undernourished.

Two possible sources of error may have to be taken into account in assessing the significance of a marginally abnormal brain:liver weight ratio. First, cerebral oedema is not uncommon in newborn infants at necropsy, usually as a complication of asphyxia, and may result in a 10% increase in brain water content (Anderson and Belton, 1972). The human infant brain is approximately 90% water in composition so that a 9-10% increase in the brain:liver weight ratio may be expected in the presence of severe brain swelling. Secondly, liver glycogenolysis proceeds rapidly in the first day of life and may also result in an increase in the ratio. In a mature, well nourished infant the liver carbohydrate concentration falls from 50mg/g to 10mg/g or less in the first 24 hours of life (Shelley and Neligan, 1966). The liver weight may therefore decrease by 4-5% and the brain:liver weight ratio increase by the same amount. However, the liver carbohydrate stores of undernourished infants are much smaller, amounting to less than 10mg/g at birth. Thus in moderately undernourished infants with marginally abnormal brain:liver weight values and intermediate quantities of liver carbohydrate, glycogenolysis is unlikely to increase the value by more than 1-2%.

Although the brain is relatively large compared with other viscera in the dysmature infant, it is probable that irreversible biochemical damage occurs in the nervous system as a result of intra-uterine undernutrition. Dysmaturity becomes evident in the last third of pregnancy which is within the period of maximal brain growth in man (Dobbing, 1970), and there is increasing experimental evidence that nutritional deprivation at the time of rapid brain growth results in a permanent deficit in the size of the brain and in the concentration of various nervous tissue constituents (see Dobbing, 1968; Winick, 1971). In addition, clinical studies have shown that infants who are small for gestational age at birth have an abnormal distribution of head circumference percentiles at follow-up examination (Davies and Davis, 1970) and that the smaller of twins has a significantly smaller head size and intelligence quotient in later childhood (Babson, Kangas, Young, and Bramhall, 1964; Churchill, 1965). It would therefore be of interest to compare the chemical composition of necropsy samples of brain from dysmature and appropriately grown infants. Results of chemical analyses of a small number of brains of malnourished children have been reported (Fishman, Prenskey, and Dodge, 1969;

Winick and Rosso, 1969; Rosso, Hormazabal, and Winick, 1970) which support the findings in experimental animals but so far there is no information available on the neurochemistry of human prenatal undernutrition. A preliminary step in such an investigation would be the separation of dysmature infants from other types of underweight infants. In this respect the brain:liver weight ratio should be helpful, for in contrast to the high values found in dysmature babies, other underweight infants as encountered in this study have values within the normal range.

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