The diagnosis of fetal microcephaly

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Of 16 fetuses in whom microcephaly was suspected, nine (56.2%) were affected with microcephaly, and seven (43.8%) were unaffected. Subsequently, nomograms with mean and SDs for biparietal diameter, occipitofrontal diameter, head perimeter:abdominal perimeter, biparietal diameter:femur length, and femur length:head perimeter were derived. With the use of the data from 27 sonograms of the 16 fetuses, different thresholds of abnormality were tested. Three standard deviations from the mean for biparietal diameter, occipitofrontal diameter, head perimeter, and femur length:head perimeter were sensitive thresholds for the diagnosis of fetal microcephaly with no false negative diagnoses. Four standard deviations from the mean for occipitofrontal diameter, head perimeter:abdominal perimeter, and femur length:head perimeter were specific tests with no false positive diagnoses. The use of multiple diagnostic tests was necessary to improve accuracy in the diagnosis of fetal microcephaly. Further clinical studies are needed to delineate more clearly optimal tests and thresholds of abnormality. (AM. J. OBSTET. GYNECOL. 149:512, 1984.)

Strictly translated, microcephaly means a small head. However, the clinical importance of the entity is its association with microencephaly (small brain) and mental retardation. At the present time, there is no universally accepted anthropomorphic definition of microcephaly. Some authors classify those infants with a head perimeter <2 SDs below the mean as having microcephaly. However, when this standard is used, the association with mental retardation is inconsistent. Three standard deviations below the mean for sex and age would appear to be a more reasonable criterion for the definition of microcephaly, as the correlation with mental retardation is stronger.[1]

There are various and heterogeneous causes of microcephaly. Although some cases are due to postnatal factors (for instance, meningitis), most are due to a cerebral growth disturbance which is present during the prenatal period. Genetic etiologies include chromosomal aberrations and single gene defects. Environmental factors such as prenatal infections (for instance, cytomegalovirus), maternal phenylketonuria, and prenatal exposure to drugs (for instance, alcohol) or radiation may play a role in the pathogenesis of microcephaly. Although craniosynostosis may result in a decreased head circumference due to deformation of skull growth, this entity is usually not classified under the rubric of microcephaly as intelligence is most often spared.

Microcephaly is often associated with other anomalies. Some have well-defined genetic or environmental causes, while in others, the precise etiology is not recognized. The heterogeneous nature of this disorder is also demonstrated by a variety of neuropathologic findings. In some cases, porencephalia, agyria, absence of the corpus callosum, or ventricular enlargement secondary to cortical atrophy may be present. However, some brains are merely small without demonstrable histopathologic changes.

Estimates of the incidence of microcephaly based on observations made at birth vary from 1 in 6250 to 1 in 8500 births. A much higher incidence, 1.6 per 1000 births, was found in the United States Collaborative Perinatal Project when infants were observed through the first year of life.

Evaluation of fetal head size and intracranial anatomy is currently possible with the use of high-resolution ultrasound. Real-time imaging facilitates examination of the moving fetus. For certain anomalies, such as hydrocephalus[2] and anencephaly,[3] the diagnostic accuracy of antenatal sonography has been established. However, the evidence that ultrasound is of similar value in the diagnosis of fetal microcephaly is far less conclusive. There have been reports of cases where sonography has been successful in the diagnosis of microcephaly,[4] unsuccessful in the early diagnosis of microcephaly,[5] and successful in the exclusion of this condition.[6] Biparietal diameter,[4] occipitofrontal diame-

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Table I. Mean and SDs of biparietal diameter as a function of gestational age

Week No.	SD above mean		Mean	SD below mean				
	+2	+1		−1	−2	−3	−4	−5
20	53	51	48	45	42	40	37	34
21	57	54	51	48	46	43	40	37
22	60	57	54	52	49	46	43	41
23	63	60	57	55	52	49	46	44
24	66	63	61	58	55	52	49	47
25	69	66	64	61	58	55	53	50
26	72	69	67	64	61	58	56	53
27	75	72	69	67	64	61	58	56
28	78	75	72	70	67	64	61	59
29	81	78	75	72	69	67	64	61
30	83	80	78	75	72	69	67	64
31	85	83	80	77	74	72	69	66
32	88	85	82	79	77	74	71	68
33	90	87	84	81	79	76	73	70
34	91	89	86	83	80	78	75	72
35	93	90	87	85	82	79	76	74
36	94	91	89	86	83	80	78	75
37	95	93	90	87	84	82	79	76
38	96	94	91	88	85	83	80	77
39	97	94	92	89	86	83	81	78
40	98	95	92	89	87	84	81	78
41	98	96	93	90	87	85	82	79
42	99	96	93	91	88	85	82	80

ter,[6] head perimeter,[5] head area,[4] head perimeter:abdominal perimeter,[4, 5] and femur length:biparietal diameter[7] have been suggested to be valuable diagnostic tests. However, there is a paucity of clinical experience to suggest which tests and which thresholds of abnormality would be most useful in the differentiation of fetal microcephaly from normocephaly. Indeed, at the present time there is no published nomogram clearly stating the measurements for biparietal diameter, occipitofrontal diameter, or head perimeter that constitute 3 SDs below the mean, the definition of microcephaly. The purpose of this communication is to report the experience of two perinatal ultrasound units with the diagnosis of fetal microcephaly. Newly derived nomograms of biometric parameters, alone and in combination, were used to examine the diagnostic accuracy of antenatal sonography.

Material and methods

Definition of study population. During the 4-year period from July 1, 1979, to July 1, 1983, microcephaly was suspected in 18 fetuses as a result of evaluations performed in the Perinatal Ultrasound Units of Yale–New Haven Medical Center and Mount Sinai Medical Center. In two instances, fetuses were delivered as stillbirths at referring hospitals and outcome information was not available. The 27 sonographic examinations performed on the 16 fetuses where outcome information was available are the data examined in this study. In each of the 16 cases, gestational age was corroborated by femur length measurement and/or a previous ultrasound examination prior to 20 weeks of gestation.

Method of study. Maternal and neonatal records were reviewed. Biparietal diameters were measured from the outer echo of the proximal skull to the inner echo of the distal skull and occipitofrontal diameters were measured from the middle of the frontal skull echo complex to the middle of the occipital skull echo complex. The cephalic index was calculated as the ratio of biparietal diameter to occipitofrontal diameter. The head perimeter was calculated from the biparietal diameter and occipitofrontal diameter,[8] and the abdominal perimeter was calculated from the abdominal diameters by the formula:

$$AP = (D_1/2 + D_2/2)\ 3.14$$

where AP = abdominal perimeter and D = diameter. For those four fetuses in whom a biparietal diameter could not be determined because of distortion of head anatomy, the widest transverse diameter of the head was measured.

Nomograms for biparietal diameter, occipitofrontal diameter, head perimeter, head perimeter:abdominal perimeter, biparietal diameter:femur length, femur length:head perimeter, and cephalic index as functions of gestational age were created. These nomograms were developed with the use of data obtained in a longitudinal study of normal fetal growth involving 695 sonographic examinations of 45 patients. The

Table II. Mean and SDs of occipitofrontal diameter as a function of gestational age

Week No.	SD above mean			SD below mean				
	+2	+1	Mean	−1	−2	−3	−4	−5
20	65	61	57	52	48	44	40	36
21	69	65	61	57	52	48	44	40
22	73	69	65	60	56	52	48	44
23	77	73	69	64	60	56	52	48
24	81	77	72	68	64	60	56	51
25	85	80	76	72	68	63	59	55
26	88	84	80	76	71	67	63	59
27	92	87	83	79	75	71	66	62
28	95	91	87	82	78	74	70	66
29	98	94	90	86	81	77	73	69
30	101	97	93	89	85	80	76	72
31	104	100	96	92	88	83	79	75
32	107	103	99	95	90	86	82	78
33	110	106	102	97	93	89	85	80
34	112	108	104	100	96	91	87	83
35	115	111	106	102	98	94	90	85
36	117	113	109	104	100	96	92	88
37	119	115	111	106	102	98	94	89
38	121	117	112	108	104	100	95	91
39	122	118	114	110	105	101	97	93
40	124	120	115	111	107	103	98	94
41	125	121	116	112	108	104	100	95
42	126	122	117	113	109	105	101	96

Table III. Mean and SDs of head perimeter as a function of gestational age

Week No.	SD above mean			SD below mean				
	+2	+1	Mean	−1	−2	−3	−4	−5
20	204	189	175	160	145	131	116	101
21	216	201	187	172	157	143	128	113
22	228	213	198	184	169	154	140	125
23	239	224	210	195	180	166	151	136
24	250	235	221	206	191	177	162	147
25	261	246	232	217	202	188	173	158
26	271	257	242	227	213	198	183	169
27	282	267	252	238	223	208	194	179
28	291	277	262	247	233	218	203	189
29	301	286	271	257	242	227	213	198
30	310	295	281	266	251	236	222	207
31	318	304	289	274	260	245	230	216
32	327	312	297	283	268	253	239	224
33	334	320	305	290	276	261	246	232
34	341	327	312	297	283	268	253	239
35	348	333	319	304	289	275	260	245
36	354	339	325	310	295	281	266	251
37	360	345	330	316	301	286	272	257
38	364	350	335	320	306	291	276	262
39	369	354	339	325	310	295	281	266
40	372	358	343	328	314	299	284	270
41	375	360	346	331	316	302	287	272
42	377	363	348	333	319	304	289	275

methods of data collection and statistical analysis for this longitudinal study as well as the derived equations for fetal head and fetal limb growth have been previously described.[9, 10] Our study population was then analyzed with these nomograms.

During the newborn period, microcephaly was diagnosed if the head perimeter was <3 SDs below the mean for gestational age, and normocephaly was diagnosed if the head perimeter was >2 SDs below the mean for gestational age. In our study population, no

Table IV. Mean and SDs of head perimeter: abdominal perimeter as a function of gestational age

Week No.	SD above mean			SD below mean				
	+2	+1	Mean	−1	−2	−3	−4	−5
20	1.43	1.34	1.25	1.16	1.07	0.98	0.89	0.8
21	1.42	1.33	1.24	1.15	1.06	0.97	0.88	0.79
22	1.41	1.32	1.23	1.14	1.05	0.96	0.87	0.78
23	1.4	1.31	1.22	1.13	1.04	0.95	0.86	0.78
24	1.39	1.3	1.21	1.12	1.03	0.94	0.86	0.77
25	1.38	1.29	1.2	1.11	1.02	0.94	0.85	0.76
26	1.37	1.28	1.19	1.1	1.02	0.93	0.84	0.75
27	1.36	1.27	1.18	1.1	1.01	0.92	0.83	0.74
28	1.35	1.26	1.17	1.09	1	0.91	0.82	0.73
29	1.34	1.25	1.17	1.08	0.99	0.9	0.81	0.72
30	1.33	1.25	1.16	1.07	0.98	0.89	0.8	0.71
31	1.33	1.24	1.15	1.06	0.97	0.88	0.79	0.7
32	1.32	1.23	1.14	1.05	0.96	0.87	0.78	0.69
33	1.31	1.22	1.13	1.04	0.95	0.86	0.77	0.68
34	1.3	1.21	1.12	1.03	0.94	0.85	0.76	0.68
35	1.29	1.2	1.11	1.02	0.93	0.84	0.76	0.67
36	1.28	1.19	1.1	1.01	0.92	0.84	0.75	0.66
37	1.27	1.18	1.09	1.00	0.92	0.83	0.74	0.65
38	1.26	1.17	1.08	1.00	0.91	0.82	0.73	0.64
39	1.25	1.16	1.08	0.99	0.90	0.81	0.72	0.63
40	1.24	1.16	1.07	0.98	0.89	0.80	0.71	0.62
41	1.24	1.15	1.06	0.97	0.88	0.79	0.70	0.61
42	1.23	1.14	1.05	0.96	0.87	0.78	0.69	0.60

Table V. Mean and SDs of femur length: head perimeter as a function of gestational age

Week No.	SD below mean					Mean	SD above mean				
	−5	−4	−3	−2	−1		+1	+2	+3	+4	+5
20	0.107	0.122	0.137	0.152	0.167	0.180	0.197	0.212	0.227	0.242	0.257
21	0.111	0.126	0.141	0.156	0.171	0.190	0.201	0.216	0.231	0.246	0.261
22	0.115	0.130	0.145	0.160	0.175	0.190	0.205	0.220	0.235	0.250	0.265
23	0.118	0.133	0.148	0.163	0.178	0.190	0.208	0.223	0.238	0.253	0.268
24	0.121	0.136	0.151	0.166	0.181	0.200	0.211	0.226	0.241	0.256	0.271
25	0.123	0.138	0.153	0.168	0.183	0.200	0.213	0.228	0.243	0.258	0.273
26	0.125	0.140	0.155	0.170	0.185	0.200	0.215	0.230	0.245	0.260	0.275
27	0.127	0.142	0.157	0.172	0.187	0.200	0.217	0.232	0.247	0.262	0.277
28	0.129	0.144	0.159	0.174	0.189	0.200	0.219	0.234	0.249	0.264	0.279
29	0.130	0.145	0.160	0.175	0.190	0.200	0.220	0.235	0.250	0.265	0.280
30	0.131	0.146	0.161	0.176	0.191	0.210	0.221	0.236	0.251	0.266	0.281
31	0.132	0.147	0.162	0.177	0.192	0.210	0.222	0.237	0.252	0.267	0.282
32	0.134	0.149	0.164	0.179	0.194	0.210	0.224	0.239	0.254	0.269	0.284
33	0.135	0.150	0.165	0.180	0.195	0.210	0.225	0.240	0.255	0.270	0.285
34	0.136	0.151	0.166	0.181	0.196	0.210	0.226	0.241	0.256	0.271	0.286
35	0.138	0.153	0.168	0.183	0.198	0.210	0.228	0.243	0.258	0.273	0.288
36	0.140	0.155	0.170	0.185	0.200	0.210	0.230	0.245	0.260	0.275	0.290
37	0.142	0.157	0.172	0.187	0.202	0.220	0.232	0.247	0.262	0.277	0.292
38	0.144	0.159	0.174	0.189	0.204	0.220	0.234	0.249	0.264	0.279	0.294
39	0.147	0.162	0.177	0.192	0.207	0.220	0.237	0.252	0.267	0.282	0.297
40	0.151	0.166	0.181	0.196	0.211	0.230	0.241	0.256	0.271	0.286	0.301
41	0.155	0.170	0.185	0.200	0.215	0.230	0.245	0.260	0.275	0.290	0.305
42	0.160	0.175	0.190	0.205	0.220	0.230	0.250	0.265	0.280	0.295	0.310

newborn infant had a head circumference between 2 and 3 SDs below the mean for gestational age.

Results

Nomograms for biparietal diameter, occipitofrontal diameter, head perimeter, head perimeter:abdominal perimeter, and femur length:head perimeter are shown in Tables I through V. For cephalic index, the mean of 80.6% and the SD of 5.0% did not vary with either gestational age or femur length.

Indications for sonography of the 16 fetuses were: discrepancy between gestational age and clinical size, 12 cases; family history of microcephaly, two cases; maternal ingestion of valproic acid, one case; evaluation

Table VI. Diagnostic accuracy of biometric parameters in the antenatal diagnosis of microcephaly

Biometric parameter	*Threshold of abnormality*	*Total No. of sonograms*	*True positive*	*True negative*	*False positive*	*False negative*
Biparietal diameter	−3 SD	27	12	3	12	0
	−4 SD	27	11	4	11	1
	−5 SD	27	8	8	7	4
Occipitofrontal diameter	−3 SD	21	6	11	4	0
	−4 SD	21	4	15	0	2
	−5 SD	21	4	15	0	2
Head perimeter	−3 SD	21	6	8	7	0
	−4 SD	21	5	13	2	1
	−5 SD	21	4	15	0	2
Head perimeter:abdominal perimeter	−3 SD	20	4	15	0	1
	−4 SD	20	3	15	0	3
	−5 SD	20	1	15	0	4
Biparietal diameter:femur length	−3 SD	24	7	5	10	2
	−4 SD	24	6	9	6	3
	−5 SD	24	6	13	2	3
Femur length:head perimeter	3 SD	19	4	13	2	0
	4 SD	19	3	15	0	1
	5 SD	19	3	15	0	1

Widest transverse diameter of the head was used when biparietal diameter could not be measured.

for postmaturity syndrome, one case. Gestational age at the time of initial examination varied from 24 to 42 weeks.

Nine of the 16 neonates were microcephalic at the time of birth. In five of these, the biparietal diameter was determined to be <−3 SDs. In four of the 16, biparietal diameter could not be determined, and the widest transverse diameter of the head was <−3 SDs for biparietal diameter. Other sonographic findings in the nine cases were: hydrocephalus, three cases; hydramnios, two cases; hypotelorism, two cases; encephalocele, two cases; renal agenesis with oligohydramnios, one case; polycystic kidneys with oligohydramnios, one case; omphalocele, one case. All anomalies were confirmed after delivery.

Seven of the 16 neonates were normocephalic at the time of birth. In each case, biparietal diameter was <−3 SDs in at least one examination. Other sonographic findings were oligohydramnios in two cases and encephalocele in one case.

The diagnostic accuracies of the various parameters at differing thresholds of abnormality are shown in Table VI. Calculation of diagnostic indices was not possible because of the small sample size and the lack of follow-up of all scans of the total population of thousands of sonograms during the 4-year time period.

Comment

In this series of 16 fetuses with ultrasonic indications of microcephaly, only nine (56.2%) were affected with microcephaly, and seven (43.8%) were unaffected. Undoubtedly, this poor predictive value was due in part to the lack of published nomograms for the diagnosis of microcephaly at the time the fetuses were scanned. Previously reported nomograms of fetal head biometry were designed to define gestational age, and the division of measurements for biparietal diameter, occipitofrontal diameter, and head perimeter into SDs below the mean had not been clearly stated.[11–15]

Biparietal diameter, occipitofrontal diameter, and head perimeter were all sensitive predictors of fetal microcephaly with no false negative diagnoses when −3 SDs was used as the threshold for abnormality. Biparietal diameter, however, was not a specific test as −3 SDs resulted in an incorrect prediction in 12 of 15 scans of fetuses with normocephaly. The presence of dolichocephaly (as suggested by a cephalic index less than −1 SD[16]) explains this finding in part. Occipitofrontal diameter and head perimeter were more specific tests. At the −4 SD threshold there were no false positive diagnoses with occipitofrontal diameter.

As the nomograms for biparietal diameter, occipitofrontal diameter, and head perimeter all require accurate gestational age, the use of a ratio of a head parameter to abdominal circumference or femur length has the advantage of reducing dependence on accurate age assessment. Biparietal diameter:femur length showed neither sensitivity nor specificity as a diagnostic test. The distortion of the fetal head probably accounts for this finding. Both head perimeter:abdominal

perimeter and femur length:head perimeter were specific tests at 4 SDs from the mean with no false positive findings. In addition, there were no false negative diagnoses with femur length:head perimeter at 3 SDs from the mean.

In conclusion, multiple diagnostic tests would appear to be necessary to optimize diagnostic accuracy in the prediction of fetal microcephaly. Although precise diagnostic indices cannot be calculated for this small sample, biparietal diameter, occipitofrontal diameter, head perimeter, and femur length:head perimeter were sensitive at 3 SDs from the mean when occipitofrontal diameter, head perimeter:abdominal perimeter, and femur length:head perimeter were specific at 4 SDs from the mean. Prospective clinical trials are needed to confirm their diagnostic value.

REFERENCES

1. Warkany J. Microcephaly, Congenital Malformations. Chicago: Year Book Medical Publishers, Inc., 1971:237-44.
2. Chervenak FA, Berkowitz RL, Romero R, et al. The diagnosis of fetal hydrocephalus. Am J Obstet Gynecol 1983;147:703.
3. Chervenak FA, Farley MA, Walters L, et al. When are third trimester pregnancy terminations morally justifiable? N Engl J Med 1984;310:501.
4. Kurtz AB, Wapner RJ, Rubin CS, et al. Ultrasound criteria for in utero diagnosis of microcephaly. J Clin Ultrasound 1980;8:11.
5. Lenke RR, Platt LD, Koch R. Ultrasonic failure of early detection of fetal microcephaly in maternal phenylketonuria. J Ultrasound Med 1983;2:177.
6. Kapp LE, Smith DW, Omenn GS, et al. Use of ultrasound in the prenatal exclusion of primary microcephaly. Gynecol Invest 1974;5:311.
7. Hohler CW, Quetel TA: Comparison of ultrasound femur length and biparietal diameter in late pregnancy. Am J Obstet Gynecol 1981;141:759.
8. Jeanty P, Romero R. Obstetrical ultrasound. New York: McGraw-Hill Book Co Inc, 1984:87-90.
9. Jeanty P, Cousaert E, Hobbins JC, et al. A longitudinal study of fetal head biometry. Am J Perinatol 1984;1:118.
10. Jeanty P, Cousaert E, Cantraine F, et al. A longitudinal study of fetal limb growth. Am J Perinatol 1984;1:136.
11. Hadlock FP, Deter RL, Harrist RB, et al. Fetal biparietal diameter: A critical re-evaluation of the relation to menstrual age by means of realtime ultrasound. J Ultrasound Med 1982;1:97.
12. Shepard M, Filly RA: A standardized plane for biparietal measurement. J Ultrasound Med 1982;1:145.
13. Kurtz AB, Wapner RJ, Kurtz RJ, et al. Analysis of biparietal diameter as an accurate indicator of gestational age. J Clin Ultrasound 1980;8:319.
14. Sabbagha RE, Hughey M: Standardization of sonar cephalometry in gestational age. Obstet Gynecol 1978;52:402.
15. Weiner SN, Plynn MJ, Kennedy AW, et al. A composite curve of ultrasound biparietal diameter for estimating gestational age. Radiology 1977;122:781.
16. Hadlock FP, Deter RL, Carpenter RJ, et al. Estimating fetal age: Effect of head shape on BPD. Am J Radiol 1981;137:83.