Prenatal Origins of Brachymesophalangia-5

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ABSTRACT As shown in 91 embryos and fetuses in the 41–235 mm crown-rump length, brachymesophalangia-5 may be identified in prenatal time. Although the ratios involving different combinations of length of mid-5 relative to other segments yield different frequencies of BMP-5, the short middle segment of the little finger is already associated with clinodactyly and developmental eccentricity as early as the ninth week of prenatal development.

Brachymesophalangia-5 (the short middle segment of the fifth finger) has been extensively studied both on a comparative basis (between populations) and on a family-line basis, in parent-child and sibling pairings. Though variously defined in relation to middle and proximal segments, and variously abbreviated as BMP and BMF, brachymesophalangia-5 proves to be especially frequent in Asiatic and Amerindian populations (Garn et al., '67; Garn et al., '72). It is often associated with cone-epiphysis mid-5, and with the clinical conditions of clinodactyly (crooked little finger) and camptodactyly (bent little finger).

So far, brachymesophalangia-5 has been investigated largely through the medium of radiography. This approach has yielded much comparative information, in population context, and much clinical information, particularly with respect to Downs' Syndrome (Trisomy 21). It is not known, however, whether brachymesophalangia-5 has prenatal origins, nor the age at earliest onset. Some authors, in fact, have suggested postnatal origins for this trait, and a possible association with malnutrition or protein-calorie malnutrition (cf. Blanco et al., '73).

Accordingly, we have investigated the presence of brachymesophalangia-5 in stained, longitudinal hand sections of 91 human embryos and fetuses, in the 41–265 mm crown-rump range. Sixty-nine of these specimens were normal by both gross and microscopic examination, and with respect to placentation. Twenty-two of the embryos and fetuses were deemed abnormal, because of gross deformities and malformation syndromes, or because they were the product of ectopic pregnancies or spontaneous abortions. All 91 specimens were of European ("white") ancestry. Other specimens of African or Asiatic derivation were excluded from the study sample.

Selected phalangeal and metacarpal lengths were measured, most using an image-splitting eyepiece micrometer, or by a projection microscope, as previously described by us (Garn et al., '75). The measurements included the lengths of the middle segments of the fourth and fifth digits, the proximal segment of the fifth digit, and the length of the second metacarpal as well as the width (diameter) of the middle segment of the fifth digit at mid-shaft. For each specimen, then, four ratios were calculated. These included the length-to-breadth ratio of mid-5, the mid-5 to mid-4 ratio, the mid-5 to proximal-5 ratio, and the mid-5 to metacarpal-2 ratio.

Using "cut-off" values of the ratios given in table 1, ten of the 69 normal embryos and fetuses fitted the definition of brachymesophalangia-5 by one or more numerical criteria. Similarly, five of the 22 abnormal specimens appeared to show brachymesophalangia-5 by one or more of the numerical definitions. Taking the different ratios one by one, between 2% and 9% of the 69 normal specimens apparently evidenced BMP, least so by the mid-5/mid-4 ratio (2%) and most often so by the classical length-to-breadth ratio of mid-5 (9%).

For the 22 abnormal specimens, including Downs' Syndrome and ectopic pregnancies, the apparent frequency of brachymesophalangia-5 ranged from zero (by the mid-5/mid-4 ratio) to 22% (by the classic length-to-width ratio). Clearly, BMP-5 could be diagnosed in embryos and fetuses, using ratios originally developed for postnatal (radiographic) material, where full bone lengths can not be visualized until epiphyseal union.

TABLE 1

Frequency of brachymesophalangia-5 in the 41–265 mm crown-rump range

Definition	Number examined	Number affected	Frequency
Normal specimens			
Mid 5/mid 4 ratio below 0.65	65	1	0.02
Mid 5/prox 5 ratio below 0.50	69	4	0.06
Mid 5/met 2 ratio below 0.25	69	5	0.07
Length/width ratio below 2.00	67	6	0.09
Abnormal specimens			
Mid 5/mid 4 ratio below 0.65	21	0	0.00
Mid 5/prox 5 ratio below 0.50	22	2	0.09
Mid 5/met 2 ratio below 0.25	22	2	0.09
Length/width ratio below 2.00	18	4	0.22

Taking the 15 "affected" embryos one by one, as shown in table 2, it is clear that the different diagnostic ratios do not fully overlap. Even though the frequencies of affected individuals are similar for the length/breadth ratio of mid-5, and the mid-5/metacarpal-2 ratio, approximately half of the specimens diagnosed by one ratio are not so identified by the other. Yet all, or nearly all, of the middle segments of the fifth digit or ray, identified by one or more of the diagnostic ratios, evidenced clinodactyly as shown by the oblique angles of the proximal or distal articular surfaces, or both.

The figure (fig. 1) pictures six of the 15 middle segments, chosen to cover the range of crown-rump lengths considered, and (in the last illustration) an example of brachymesophalangia-5 in a fetus with Downs' Syndrome. Clearly, shortening, broadening and obliquity of the articular surfaces are all evident well before true bone formation. These photomicrographs further show the asymmetry of the affected segment, and the eccentricity of the growth "center," to a degree not previously attained in radiographic representations.

Brachymesophalangia-5 therefore appears to have its origins in the early prenatal period, as early as the ninth week, and with the manifestation of *clinodactyly* fully developed, as judged from the obliq-

TABLE 2

Bone-to-bone relationships in prenatal examples of brachymesophalangia-5

Specimen number	Crown-rump length	Mid 5/mid 4 ratio	Mid 5/prox 5 ratio	Mid 5/met 2 ratio	Length/width ratio
		Normal specimens			
708	41	0.70	0.56	0.28	1.73*
1198	61	0.79	0.59	0.24*	2.26
1352	66	0.81	0.49*	0.25	1.63*
1419	68	0.81	0.57	0.24*	1.87*
1184	69	0.82	0.61	0.31	1.97*
1424	94	0.68	0.47*	0.24*	1.94*
1443	130	0.69	0.56	0.24*	2.69
1445	165	0.76	0.55	0.28	1.85*
1527	180	0.63*	0.44*	0.22*	2.31
1367	188	†	0.48*	0.29	1.93*
		Abnormal specimens			
1432	54	0.79	0.53	0.27	1.61*
1187	60	0.76	0.60	0.26	1.90*
1001	80	0.71	0.48*	0.25	1.71*
1440	127	0.70	0.52	0.23*	3.06
1525	155	0.71	0.44*	0.21*	1.97*

* Asterisks denote specimens that fit the criterion of brachymesophalangia by the ratio used. The symbol † denotes one ratio that could not be completed because of technical limitations.

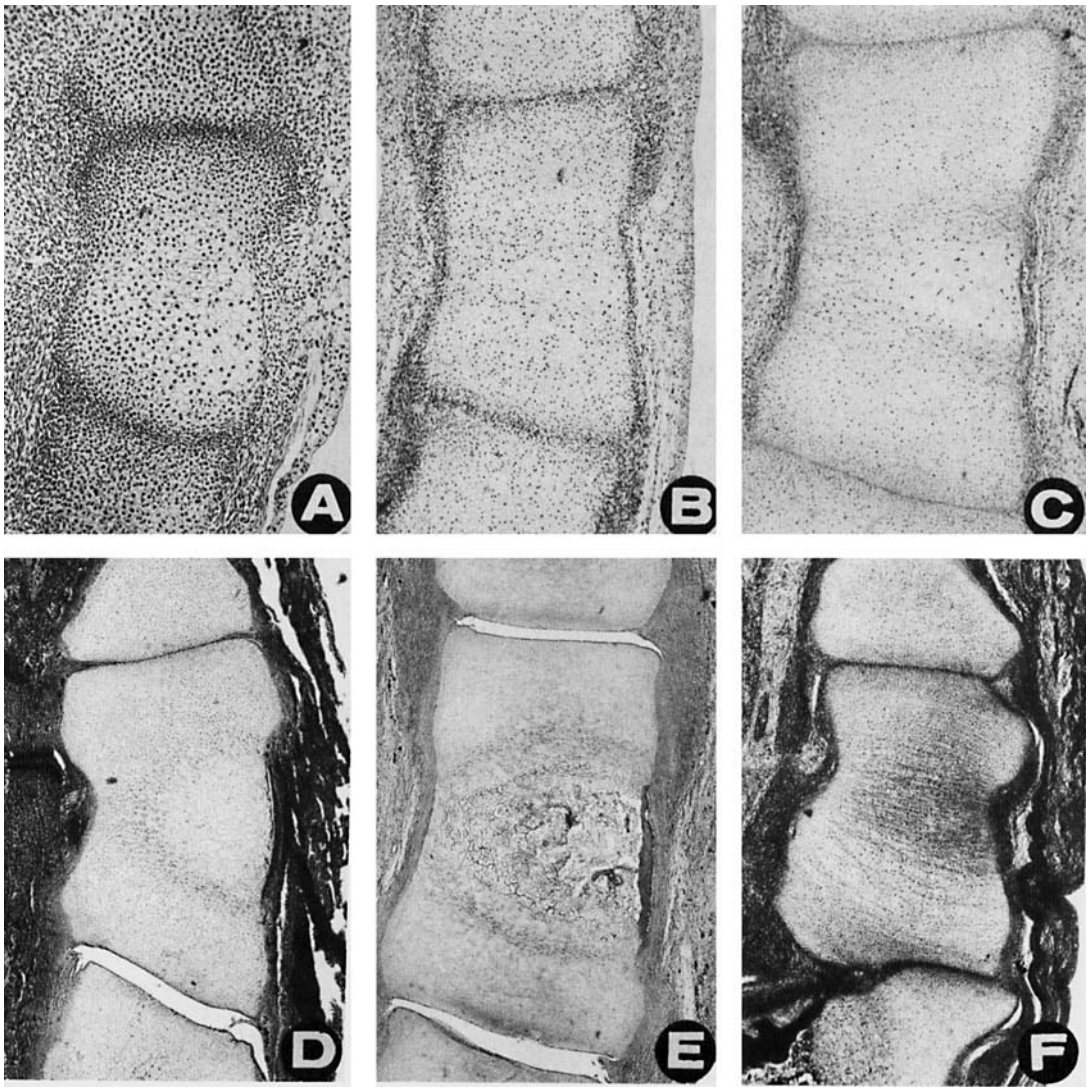

Fig. 1 Postero-anterior photomicrographs showing brachymesophalangia-5, clinodactyly and developmental asymmetry in the middle segment of the fifth finger in six human embryos and fetuses in the 41–165 mm crown-rump length range. Examples A through E show brachymesophalangia-5 in normal specimens while F (lower right) pictures BMP-5 in Downs' Syndrome. Note that both chondral hypertrophy and bone collar formation (as shown in D,E) are developmentally advanced on the ulnar (concave) side of the middle phalanx, consistent with the eccentricity of form. These six examples correspond to identifications 708, 1419, 1352, 1424, 1445 and 1525 in table 2 and represent magnifications of × 22.4 (A through C), × 9.1 (D,E) and × 10.5 (F).

uity of the articular surfaces. This study of brachymesophalangia-5 in embryos and fetuses shows the complications that arise from different diagnostic ratios, and emphasizes the need for a single criterion that may be employed from the 41 mm crown-rump length through to adulthood. Although the cut-off values of all of the ratios could be adjusted to fit the fact that the full bone lengths are visible on the histological sections, and to yield approximately similar frequencies of BMP-5, the different ratios do not identify the same individuals.

In summary, broad and short middle segments of the fifth digit, along with clinodactyly and eccentric development of mid-5 may be seen in prenatal time, as early as the ninth week of development. The ratios, individually presented, and the photomicrographs together make it clear that BMP-5 (or BMF-5) is not limited to the postnatal period and that events subsequent to birth need not be postulated as a proximate cause in the majority of cases.

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