Autosomal Dominant Microcephaly With Normal Intelligence, Short Palpebral Fissures, and Digital Anomalies

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We describe a family segregating an autosomal dominant mutation producing a syndrome comprising microcephaly with normal intelligence and short palpebral fissures together with variable signs including thumb hypoplasia, shortness of the middle phalanges of the second and fifth fingers, small feet, a gap between the first and second toes, and mild syndactyly of the toes or fingers. A characteristic radiologic finding in our family is thinning of the proximal end of the first metacarpal and shortening of that metacarpal. The severity of these findings was asymmetric in our patients. This syndrome is similar to patients described by Brunner and Winter [1991: J Med Genet 28: 389–394], Feingold [1975: Synd Ident 3:16–17, 1978: Hosp Prac 13:44–49], and König et al. [1990: Dysmorphol Clin Genet 4:83–86]. Am. J. Med. Genet. 71:150–155, 1997.

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KEY WORDS: microcephaly; autosomal dominant; digital anomalies; thumb hypoplasia; short palpebral fissures; syndactyly

INTRODUCTION

We describe a family with apparent autosomal dominant transmission of microcephaly with normal intelligence and short palpebral fissures; however, there is considerable variability and individual asymmetry in the defects of the limbs. The major limb anomalies are hypoplastic, slender thumbs with limited flexion at the distal interphalangeal joints of thumbs and some fingers, thin proximal first metacarpals, and short middle phalanges of the index and fifth fingers. We present radiographs and a metacarpophalangeal profile analysis to facilitate the identification of other patients with this syndrome.

CLINICAL REPORT

The pedigree is shown in Figure 1. Table I summarizes the abnormalities identified in affected family members [Hall et al. 1989].

The propositus, individual III-3 (Fig. 2B), was born at 38 weeks of gestation to a 30-year-old G 7P2 white woman by spontaneous vaginal delivery after artificial rupture of membranes. Alcohol, tobacco, and drug abuse were denied. The pregnancy was uncomplicated. Apgar scores were 9 at one minute and 9 at 5 minutes. At birth, the child weighed 3,640 g (70th centile), length was 52 cm (55th centile), and the head circumference (OFC) was 32 cm (5th centile). She smiled at 2 months and began babbling at 3 months. At 3 months OFC was 36 cm (< 3rd centile or approximately 50th centile for an 11-week-old infant). Her head appeared microcephalic with biparietal narrowing. The anterior fontanel was open and there was a prominent lambdoid ridge. Skull films showed open cranial sutures. The inner canthal distance was 2 cm, between the 3rd and 25th centiles for age. Outer canthal distance was 5.2 cm, between the 3rd and 25th centiles. The ears were 4.5 and 4.6 cm long (between the 75th and 97th centile) and were normal in shape and position. There were no preauricular pits or tags. She had a broad nasal bridge with normal shape and position to the nose. The palate showed no evidence of clefting. The neck was short. Clavicles were completely formed bilaterally. Cardiovascular exam showed a regular rate and rhythm with no murmurs. Extremity anomalies are listed in Table I.

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There was no nail dysplasia. There was normal mobility of more proximal upper or lower limb joints. The right thumb showed the greatest restriction of movement. At 7 months the right and left total hand lengths were 8 cm (25th–50th centile). The middle finger length was 3.4 cm on the right and 3.3 cm on the left (25th–50th centile). Radiographic examination of the arms and legs showed normal osseous structures with no evidence of radioulnar synostosis. Both femoral ossification centers were present and symmetric. In the feet, the middle and distal phalanges of all toes appeared short. There was no evidence of ossification of the carpal bones at age 3 months, which suggested a minimal delay in bone maturation (Fig. 3B). There is thinning of the proximal end of the first metacarpal and shortening of the 2nd and 5th middle phalanges. Skull films at 7 months showed open cranial sutures.

Her brother, III-2 (Fig. 2C,E), was 4 and 2/12 years old at examination and was born at 39 weeks by spontaneous vaginal delivery. His Apgar scores were 7 at 1 minute and 8 at 5 minutes. The pregnancy was uncomplicated. Birth weight was 2,300 g (< 3rd centile) and length was 49 cm (25th centile). He walked unassisted at 11 months. His teeth began to erupt at 9 months. It was not until 2 1/2 years of age before his first words were noted and improvement was observed after speech therapy for 5 to 6 months.

On physical examination, height was 98.1 cm (10th centile), arm span was 97 cm, weight was 16.0 kg (25th–50th centile), and OFC was 46.3 cm (< 3rd centile or approximately 50th centile for a 10-month-old boy). The child appeared microcephalic with prominent lambdoid ridges and a low anterior hair line (Fig. 2C). The anterior and posterior fontanels were closed and there were no scalp or cranial lesions. The inner canthal distance was 2.7 cm (50th centile). The interpupillary distance was 4.3 cm, which is between the 3rd and 25th centiles. The outer canthal distance was 6.4 cm (< 3rd centile). Ear shape, size, and position were normal. There were no preauricular pits or tags. The child had a normal palate and normal teeth. He had a normal penis with descended testes, but slightly hypoplastic scrotum. There were no sacral dimples or pits. The back was normally curved. Thumb movement was restricted in flexion bilaterally particularly at the distal interphalangeal joints. The right and left hand lengths

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<th>TABLE I. Affected Family Member Anomalies</th>
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<td>OFC &lt; 3rd centile</td>
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<td>Palpebral fissure lengths &lt; 3rd centile</td>
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<td>Epicanthal folds</td>
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<td>Hypoplastic thumb(s)</td>
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<td>Inflexible DIP joints thumbs or fingers</td>
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<tr>
<td>Single palmar crease</td>
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<td>Mild syndactyly fingers ⅔</td>
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<td>Clinodactyly fingers 2, 4 and/or 5</td>
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<td>Short middle phalanx second finger</td>
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<td>Single crease fifth finger/short fifth middle phalanx</td>
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<td>Foot length &lt; 3rd centile</td>
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<td>Pes planus</td>
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<td>Relatively broad great toes</td>
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<td>Gap between 1st/2nd toes</td>
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<td>Mild syndactyly toes ⅔</td>
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*No radiographs were available for these family members.*
were 11.6 and 11.3 cm, respectively (3rd–25th centile). The right and left middle finger lengths were 4.9 and 5.1 cm, respectively, which is approximately the 50th centile. There was no nail dysplasia. There was no restriction of movement or osseous abnormality of more proximal joints of the limbs. Radiographic examination of the hands revealed asymmetric thinning of the proximal portion of the first metacarpal, and marked shortening of the 2nd and 5th middle phalanges (Fig. 3C). Skeletal survey at birth showed open cranial sutures.

Individual III-1 had normal developmental history, growth, and physical findings. Her OFC was 42.5 cm (90th centile) at age 4-1/4 months. At 6-1/2 years head circumference was 53 cm (97th centile). Her palpebral fissure lengths were 2.4 cm bilaterally (< 5th centile). No abnormality of her hands or feet was identified.

Individual II-1 (Fig. 2A,D), the father of the children
described above, was 30 years old at the time of examination. He had normal development as a child. He finished 12th grade as an average student and is currently a printing press assistant. Height was 174.8 cm (25th–50th centile), span was 174.5 cm, weight was 85.4 kg (>97th centile), and OFC was 52.2 cm (< 3rd centile). His inner canthal distance was 3.1 cm (50th–75th centile). The interpupillary distance was 5.7 cm (50th centile) and palpebral fissure lengths were 2.4 cm (< 3rd centile). Ear lengths were normal. The nasal septum was deviated slightly to the left. Teeth were normal. Hand and middle finger lengths were normal bilaterally. He was left handed and the left thumb was larger than the right. He had hypoplastic right thenar muscles. The right thumb could not be flexed at the distal interphalangeal joint. The left thumb had normal creases and was flexible at the distal interphalangeal joint. There was no nail dysplasia. He had a slightly asymmetric chest with the right side being larger than the left. His back was normally curved. Chromosomes were normal (46, XY) without anomaly of 13q. Radiographic examination of the hand (Fig. 3A)
is shown. There is shortening of the first metacarpal and flattening of its distal end.

Individual II-2 graduated from high school as an average student and took a business course for 9 months after graduation. She received speech therapy as a child. Her OFC at age 28 was 49.5 cm (< 3rd centile) and height was 163 cm (50th centile). The inner canthal distance was 2.8 cm (25th centile), outer canthal distance was 7.5 cm (< 3rd centile), and the interpupillary distance was 5 cm (3rd centile). There was no clinical thumb hypoplasia. Feet measured 23 cm bilaterally (25th centile).

Individual III-4 walked at 12 months, spoke words at 18 months, and talked in sentences at 3 years. He was 4-10/12 years at the time of exam. OFC was 45 cm (< 3rd centile) and height was 107 cm (50th centile). Palpebral fissures were 2.0 cm (much less than 3rd centile). Total hand lengths were at the 25th centile. He had normal hands and feet.

Individual III-5 was 8-1/2 years old at the time of examination. She had a normal developmental history and is doing well in school. OFC was 46.25 cm (< 3rd centile) and height 129 cm (50th centile). Palpebral fissure lengths were 2.1 and 2.2 cm (< 3rd centile).

Individual I-2 had an OFC of 54.75 cm (50th centile) and normal hands and feet.

Individuals I-1 and II-3 could not be examined; information derived from I-2 suggested that they were similarly affected. Individual II-3 has a small head, a unilateral small thumb, and history of a tracheoesophageal fistula.

Figure 4 presents a Poznanski metacarpophalangeal profile analysis for II-1, III-2, and III-3.

DISCUSSION

We have described a family with autosomal dominant microcephaly with normal intelligence and variable digital anomalies. Affected individuals have microcephaly (< 3rd centile) and short palpebral fissures. No evidence for craniosynostosis could be found on skull films of two affected individuals (III-2 and III-3). Two relatives required speech therapy but there is no evidence for learning disability or mental impairment. Only one relative had microcephaly and short palpebral fissures without hand or foot anomalies (III-4). Thumb hypoplasia was unilateral, bilateral, or absent. When present, the phalanges and the first metacarpal were affected and there was often limitation of flexion of the distal interphalangeal joints. These individuals had asymmetric shortening of the first metacarpal and a distinctive thinning of the proximal first metacarpal. Clinoacdy of the second and fifth fingers was common and is due to hypoplasia of the second phalanx of these digits. A concomitant reduction in the number of creases of these digits also was observed. The feet were often short (< 3rd centile) especially relative to height (often between the 25th and 50th centile) and there was variable syndactyly between toes or fingers. Some affected relatives had a gap between the first and second toes and a broad great toe.

There are numerous disorders combining microcephaly and digital anomalies. Many can be excluded on the basis of an autosomal recessive or X-linked inheritance and/or distinguishing findings [Hunter, 1993; McKusick, 1996; Opitz and Holt, 1990]. Since microcephaly was the consistent anomaly in affected relatives, a review of the literature with these key words generated a short list of potentially related syndromes. Autosomal dominant microcephaly syndromes were discussed briefly by Winter [1993, Reports by Feingold [1975, 1978], Brunner and Winter [1991], and König et al. [1990] described collectively a syndrome of tracheoesophageal fistula, duodenal atresia, hypoplastic thumbs, brachymesophalangy, 4/5 syndactyly of the...
toes, and short palpebral fissures with microcephaly that appears to be similar to the family described here. The similarities between the cases in the literature and those reported here make it likely that the differences observed probably represent the spectrum of this syndrome. While most patients in the literature have normal early development, it is important to point out that in family 1 of Brunner and Winter (1991), 5/7 persons attended special schools for learning problems or disabilities. No formal testing was performed to determine the individual learning difficulties necessitating this type of environment. In addition, no thumb hypoplasia was present in any relative, the degree of microcephaly was not as severe as reported here, and there was marked syndactyly of toes 4/5 in 12/13 relatives in that report. Whereas the hallmark of the families described by Brunner and Winter were clinodactyly of the fifth fingers and 4/5 toe syndactyly, the digital anomalies were the most variable in our patients. Moreover, microcephaly, clearly much less than the 3rd centile, was always present in our patients, whereas at least two affected persons in family 1 were at the 10th centile for OFC.

The mean pattern profile for our family showed similarity to the mean pattern of the two hands published by König et al. (1990) (r = 0.68) and to that of the girl in Feingold's report (1975, 1978) (r = 0.91), which was calculated from the radiograph of the patient (which was kindly sent to us by the author). In addition, the thinning of the proximal portion of the first metacarpal seen in most of our family members was also evident on the radiograph we received from Dr. Feingold. However, it was not evident in the radiograph published by König et al (1990) and was in some of our cases milder on one side than the other. This may be a useful sign as it is not seen in many syndromes with first metacarpal hypoplasia.

Approximately 30% of the relatives reported by Brunner and Winter (1991) and the boy reported by Feingold (1978) had tracheoesophageal fistula and/or duodenal atresia. In two patients, this was associated with polyhydramnios. Polyhydramnios or duodenal atresia was not part of the history of any of the patients we examined. One individual, II-3, has a history of tracheoesophageal fistula. If the family described here is taken together with previous reports, the risk for TEF and/or duodenal atresia is 8/29 or approximately 28%.

The summary of Brunner and Winter (1991) listed 21 patients affected with the disorder, of which 9 were male and 12 were female. The family we describe consists of three males and three females known to be affected, and two other males likely to be (shaded in Fig. 1). The data support autosomal dominant inheritance with equal numbers of affected males and females. The occurrence of four miscarriages in one branch of the family reported here does not appear related to the inheritance of the mutation, since no miscarriages were reported for II-2 or the spouse of II-3.

All karyotypes of reported patients were normal. In some, attention was directed to 13q due to the similar occurrence of hypoplastic thumbs, syndactyly of toes 4/5, clinodactyly of the fifth fingers, microcephaly, and short palpebral fissures (among other problems) in patients with deletions of chromosome 13q22-qter (Schinzel, 1984). That search failed to show evidence for deletion or rearrangement. Similarly, we found no detectable deletion. Efforts to determine the genetic defect responsible for this syndrome might begin by determining whether the mutation is linked to selected chromosome 13q markers.

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REFERENCES


