American Journal of Medical Genetics Supplement 6:3–16 (1990)

Broad Thumb-Hallux (Rubinstein-Taybi) Syndrome 1957–1988

J. H. Rubinstein
University Affiliated Cincinnati Center for Developmental Disorders, Cincinnati, Ohio

This presentation records the early history of the description of the broad thumb-hallux syndrome and attempts to update the current state of knowledge about this syndrome.

Information was collected and reviewed on 571 individuals from the world literature, from communications with colleagues and families of affected individuals, and from personal observation. The diagnosis was established in most cases by confirming the concurrence of the constellation of major diagnostic criteria, including broad short terminal phalanges of the thumbs and halluces, with or without angulation deformity; characteristic facial appearance with beaked or straight nose, antimongoloid slant of palpebral fissures, apparent or clinical hypertelorism and grimacing smile; stature and head circumference (OFC) below 50th centile; mental, motor, social, and language retardation; stiff awkward gait; and incomplete or delayed descent of testes in males. Information on associated clinical factors, familial occurrence, and cytogenetic findings is presented

KEY WORDS: broad thumb-hallux syndrome, Rubinstein-Taybi syndrome, mental retardation, broad thumb syndrome

INTRODUCTION

In 1957, I evaluated a 3½-year-old girl with unusual facial appearance and broad thumbs and great toes. The following year, I saw a 7-year-old boy with similar manifestations. These 2 unrelated children resembled each other so closely as to suggest that they both had the same syndrome. In 1959–1960, assisted by the Federal Children's Bureau, I tried to find additional cases of this possible "syndrome" by disseminating the photos (Fig. 1) and clinical data to other Children's Bureau clinics for children with mental retardation; however, there were no responses. At the suggestion of Dr. Josef Warkany of Cincinnati, Dr. W.C. Marshall of Great Ormond Street sent me photos in January 1960 of 2 English children with similar clinical findings. Because of their radially angulated thumbs, not present in the 2 American children, I deferred accepting them as examples of the "syndrome." Later that same year, I saw an 8½-year-old girl who resembled the first case. In 1961, through the courtesy of Dr. Fred Silverman, Director of Pediatric Radiology at Children's Hospital in Cincinnati, I received information on a 3-year-old boy in Oklahoma City from Dr. Taybi.

In October of 1962, Dr. Taybi reported at the annual meeting of the Society for Pediatric Radiology on the 5 children we had seen to date. In May of 1963 at the annual meeting of the American Association on Mental Deficiency, I reported on a total of 7 children, 2 girls and 5 boys, with broad thumbs and great toes together with distinctive facial appearance, growth retardation, mental retardation, and cryptorchidism in males as a possible syndrome. In June 1963, Dr. Taybi and I published these findings in the *American Journal of Diseases of Children* [Rubinstein and Taybi, 1963].

Dr. Coffin published his series in 1964 [Coffin, 1964], and Dr. Johnson published his series in 1966 [Johnson, 1966]. In 1968, I reported on a total of 114 individuals with the syndrome at the First Conference on the Clinical Delineation of Birth Defects in Baltimore [Rubinstein, 1969], including cases gathered from almost 50 publications on the syndrome.

Ten years after our initial publication, in a letter to the editor, entitled "Fatherhood of the So-Called Rubinstein-Taybi Syndrome," Dr. Matsoukas [Matsoukas, 1973] stated that in 1957, Michail et al. from Athens first published a case report in a French orthopedic journal [Michail et al., 1957]. This was an excellent description with photographs of a 7-year-old Greek boy with radially deviated arched thumbs secondary to dorsal dislocation of a broad distal phalanx on a triangularly shaped proximal phalanx. Associated findings included mental retardation, "comical" face, long "Cyrano-type" nose, muscular hypotonia, cryptorchidism, slightly "turgid spindle" legs, flat feet, physical underdevelop-

Received for publication February 6, 1989; revision received September 18, 1989.

Address reprint requests to Jack H. Rubinstein, M.D., Director, University Affiliated Cincinnati Center for Developmental Disorders, Pavilion Building, Elland and Bethesda Avenues, Cincinnati, OH 45229.

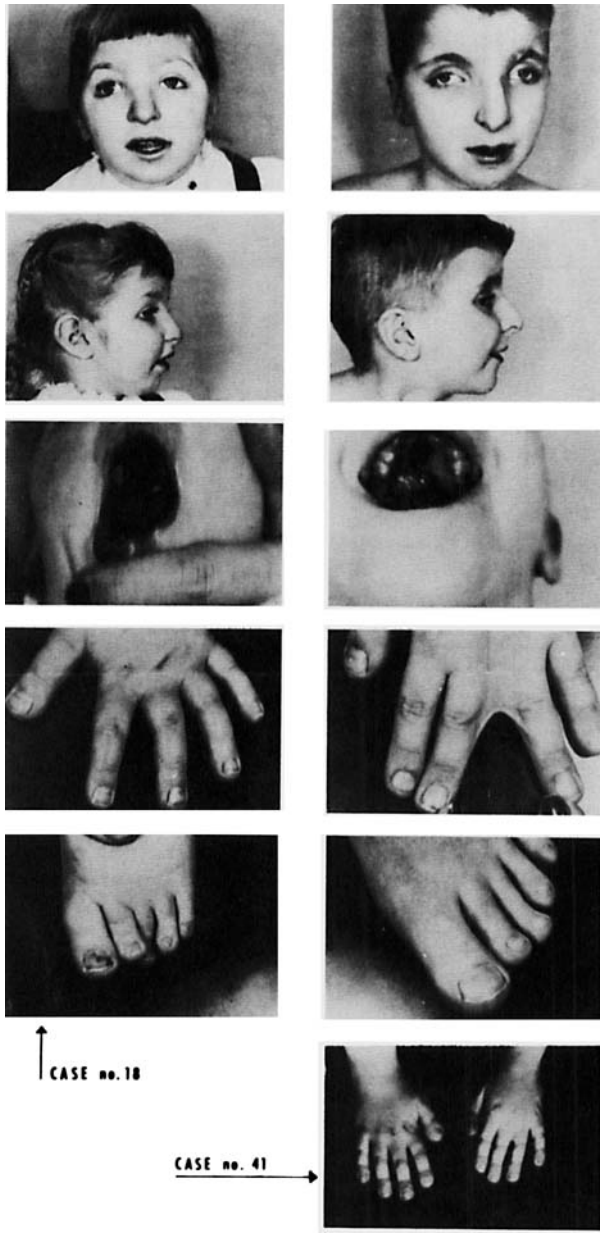


Fig. 1. Photographs of patients 1 and 2 with BTHS as distributed in 1959–1960 to other Children's Bureau clinics for children with mental retardation.

ment, and funnel chest. In retrospect, he clearly had the same syndrome that Taybi and I described in 1963.

The present paper summarizes selected findings in a total of 571 individuals thought to have the broad thumb-hallux syndrome (BTHS). The series represents 342 cases collected from 221 articles in the literature; 64 personally examined; and 165 from personal communications from colleagues and families. Several reports in the literature of the last 10 years were excluded when I had a significant question about the diagnosis. This series still includes a number of individuals with whose diagnosis I am not totally comfortable.

RESULTS

The 571 individuals were from 40 countries. Two hundred sixty-three (46%) were female and 308 (54%) male. Fourteen were black, 23 Japanese, 2 Chinese and the rest Caucasian. Ages ranged from one day to 62 years with a median age at the time of reporting of 4½ years. Forty-four individuals are known to have died.

Parental age, prenatal course, and birth history show no consistent trends.

Medical history (Table I) was often characterized by feeding difficulties, neonatal distress, and/or recurrent respiratory infections. In some children, these problems may be related to gastroesophageal reflux [Grunow, 1982], which may require surgical treatment. There were 2 children with sleep apnea, one associated with gastroesophageal reflux. There was one child with an episode of apnea with feeding. Stirt [1981] warns of the risk of aspiration during anesthesia. Chronic constipation was often a problem.

Stridor or hoarseness was noted in 8 infants, low-pitched or husky voice in 4 children, and a history of a weak whimper or abnormal cry in approximately 40 infants. Six children showed vocal cord paralysis, laryngospasm, or other abnormalities of the glottis and surrounding tissues.

Stature and bone age were <50th centile and stature was often <5th centile (Table II). In a series of 19 men and 23 women with BTHS 18 years of age or older, average and median adult height was 61½ inches for men (50th centile for boys 13 years of age) and 58 inches for women (50th centile for girls 11½ years of age).

When it could be evaluated, retardation was noted in mental, motor, language, and social spheres and in 74% of individuals the IQ was under 50 (Table II).

Electroencephalographic abnormalities were noted in 66% of cases; however, seizures were recorded in only about 25%. Deep tendon reflexes were hyperactive in about 50% of individuals (Table II). There was absence or hypoplasia of the corpus callosum detected at autopsy or by neuroradiographic studies in 15 of 89 cases [Neuhäuser and Schulze, 1968; Lamy et al., 1967; Coffin, 1964; True and Rubinstein, 1968; Pogacar and Nora, 1970; Fukanaga et al., 1969] (Table II) Other neuropathological findings were absence of the septum pellucidum and hippocampal commissure, abnormally formed and oriented lateral ventricles, malgyration, and microscopic abnormalities of the cytoarchitecture of the cerebral cortex.

Head circumference (OFC) was <50th centile, and microcephaly (<2nd centile) occurred in 94% (Table II). Hydrocephalus was recorded in 7 individuals: 3 with Arnold-Chiari malformation and myelomeningocele, 2 with Dandy-Walker cyst, and 2 with brain tumor. Ten other individuals had ventricular dilatation in association with microcephaly.

The anterior fontanel tended to be large or was reported as late in closing, and by roentgenogram, parietal foramina (Fig. 2) were present in 29% of 180 individuals (Table II).

Minor facial anomalies included (Table III): prominent forehead, beaked or straight nose, broad nasal

TABLE 1. Frequency of Findings in 571 Individuals With Broad Thumb-Hallux (BTHS) Syndrome: Prenatal, Birth, and Early History

Finding	Present (%)	Absent	Not stated
Birth weight 2,500 g or less	89 (20)[a]	362	120
Maternal age 35 years or older	44 (11)	368	159
Paternal age 35 years or older	79 (21)	292	200
Polyhydramnios	49 (20)	197	325
Feeding difficulties in infancy[b]	287 (77)	88	196
Neonatal distress or recurrent respiratory infections[b]	324 (78)	93	154
Constipation	139 (54)	117	309
Allergy	51 (31)	116	404

[a] Percentage is determined by the No. of cases in which the finding is present, with the denominator being the No. of cases in which the finding is stated as present or absent.
[b] Occurs in 2/3 or more of cases in which finding is recorded.

TABLE II. Frequency of Findings in BTHS: Anthropometric, Cognitive, and Neurologic

Finding	Present (%)	Absent	Not stated
Stature <50th centile[a]	457 (93)	36	78
Stature <5th centile[a]	343 (78)	94	134
Bone age <50th centile[a]	176 (74)	63	332
Mental, motor, language, and social retardation[a]	512 (99)	4	55
IQ over 50	104 (27)	288	179
IQ under 50[a]	289 (74)	104	178
Electroencephalographic abnormalities[a]	153 (66)	80	338
Seizures	80 (28)	207	284
Deep tendon reflexes hyperactive	154 (53)	138	279
Absent/hypoplastic corpus callosum (PEG, CT, NMR, or autopsy)	15 (17)	74	482
Head circumference <50th centile[a]	446 (95)	24	101
Head circumference <2nd centile[a]	304 (94)	18	249
Foramen magnum large	56 (50)	56	459
Anterior fontanel large or late in closing	134 (62)	83	345
Parietal foramina	53 (29)	127	391

[a] Occurs in 2/3 or more of cases in which finding is recorded.

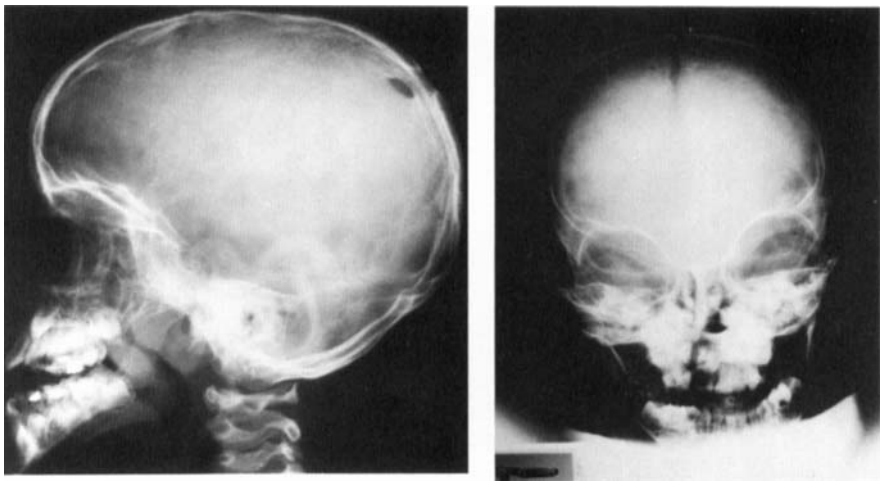


Fig. 2. Skull parietal foramina in BTHS. **a:** Lateral view of a skull in a 6½-year-old boy showing a large parietal foramen. **b:** Frontal view of skull showing small right parietal foramen in a 3-year-old girl.

bridge, nasal septum extending below nasal alae, apparent or clinical hypertelorism, antimongoloid slant of palpebral fissures, heavy or highly arched eyebrows, epicanthi, and minimal abnormalities in rotation, position, size, or shape of ears. The mouth appeared small but more commonly the upper lip appeared thin, and there was mild retrognathia (Table III). The grimacing smile, or as reported by Michail et al. [1957], "a comical face," (Fig. 3) was commented on in 76% of 189 individuals.

Facial manifestations were less characteristic neonatally and in infancy than at a later age and changed with increasing age (Figs. 3, 4). Individuals with the BTHS who were black could have been underreported since facial findings were much less characteristic (Fig. 5) [Filippi, 1969; Mourigan et al., 1975; Ziring et al., 1974; Sinnette and Odeku, 1968].

The palate was reported as appearing highly arched with wide alveolar ridges (Fig. 6) in 93% (Table III). Ten individuals were described as having a bifid uvula, 4 a submucous cleft, and one both; 3 a cleft hard palate, 2 a cleft soft palate, and one both; one a cleft lip and palate; and one a short soft palate. Dental irregularity and overcrowding were described in 67% of individuals. Talon cusps or markedly enlarged cingula on the permanent maxillary incisors have been reported [Gardner and Girgis, 1979; Kinirons, 1983]. Occasionally there was a progressive distortion of the mid-face which accentuated the dysharmony between upper and lower jaw producing an almost grotesque facial appearance.

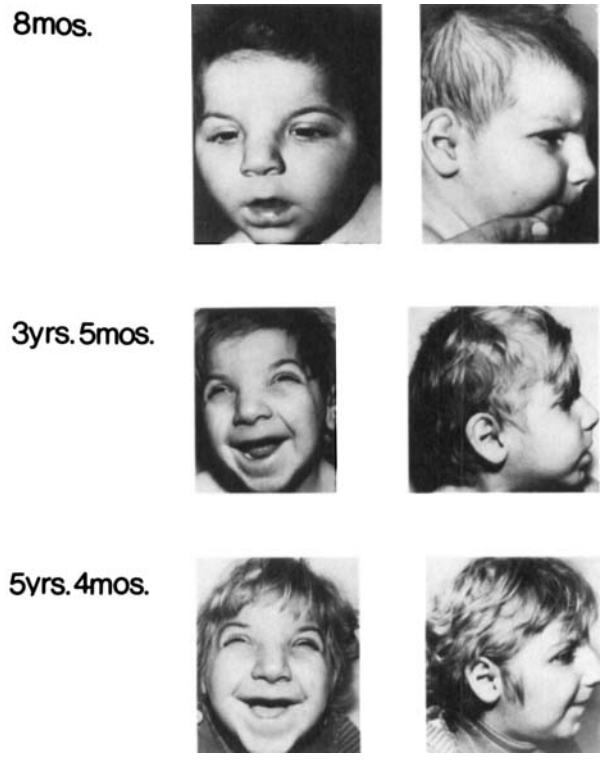


Fig. 3. Face of boy with BTHS showing that the characteristic face becomes more prominent with increasing age and illustrating typical smile.

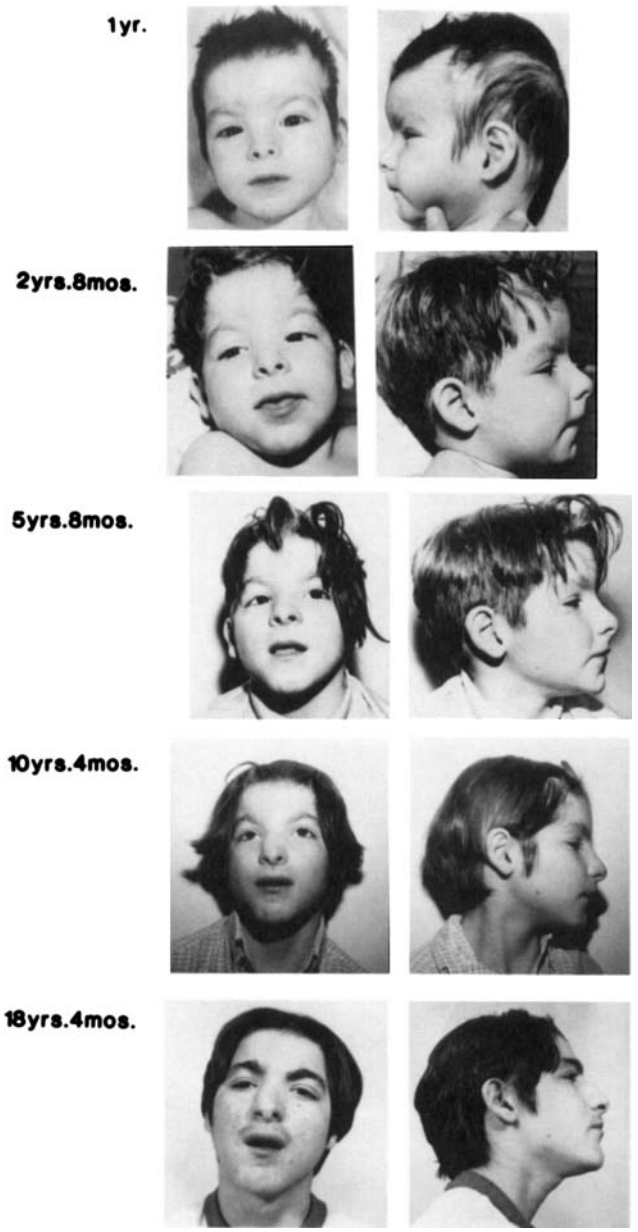


Fig. 4. Face of boy with BTHS showing that the manifestations become more characteristic of the syndrome after age 1.

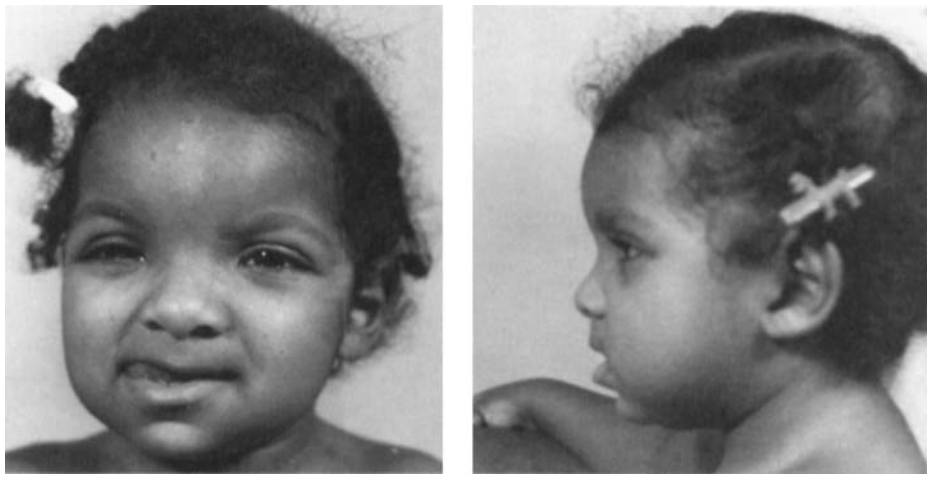
A large variety of ophthalmologic findings have been reported including (Table IV) those that form part of the facial gestalt as well as strabismus, refractive errors, ptosis (rarely secondary to Marcus Gunn jaw winking), and nasolacrimal duct obstruction [Völcker and Haase, 1975]. Colobomata, cataracts, intrauterine keratitis/corneal leukoma/congenital corneal scar, and glaucoma have been reported [Ziring et al., 1974].

Broad short thumbs and/or halluces were arbitrarily considered a requisite for diagnosis and were therefore present in 100% of cases (Table V). Unfortunately, adequate standards still do not exist to help decide when thumbs and great toes are sufficiently broad to be considered abnormal in borderline cases.

TABLE III. Frequency of Facial Findings in BTHS

Finding	Present (%)	Absent	Not stated
Forehead prominence	223 (60)	148	200
Nasal bridge broad[a]	372 (86)	86	113
Nose beaked or straight[a]	486 (93)	39	46
Nasal septum below alae[a]	331 (78)	92	148
Hypertelorism, apparent[a]	353 (83)	73	145
Eyebrows, heavy or highly arched[a]	306 (68)	141	124
Long lashes	158 (51)	150	263
Epicanthi[a]	307 (69)	136	128
Palpebral fissures, antimongoloid slant[a]	473 (90)	53	45
Ears: minimal abnormalities in position, rotation, size, or shape[a]	372 (81)	86	113
Mouth, small appearing	225 (56)	174	172
Retrognathia, mild[a]	298 (75)	100	173
Smile, grimacing[a]	144 (76)	45	382
Palate highly arched in appearance[a]	454 (93)	33	84
Dental abnormalities[a]	124 (67)	60	387

[a] Occurs in 2/3 or more of cases in which finding is recorded.



a b

Fig. 5. Facial characteristics in 25-month-old black girl with BTHS. The clinical manifestations are less characteristic than those in white individuals with BTHS.

TABLE IV. Frequency of Ophthalmologic Findings in BTHS

Finding	Present (%)	Absent	Not stated
Strabismus[a]	292 (71)	126	153
Refractive error	124 (56)	97	350
Ptosis	92 (29)	230	249
Nasolacrimal duct obstruction	80 (37)	134	357

[a] Occurs in 2/3 or more of cases in which finding is recorded.

The broad thumbs were usually a readily recognizable abnormality and have been described as spatulate, short and stubby, clubbed, flat and wide, or simply large. They were often noted to be unusual neonatally. In comparison with a normal thumb, they are broad, and in some cases, flat with shortness of the distal phalanx. The thumbnail may be similarly flat and short (Fig. 7a).

The distal phalanx of the thumb was short and wide when the radiographs were properly taken with the thumbs pressed flat. There was often a small hole in the

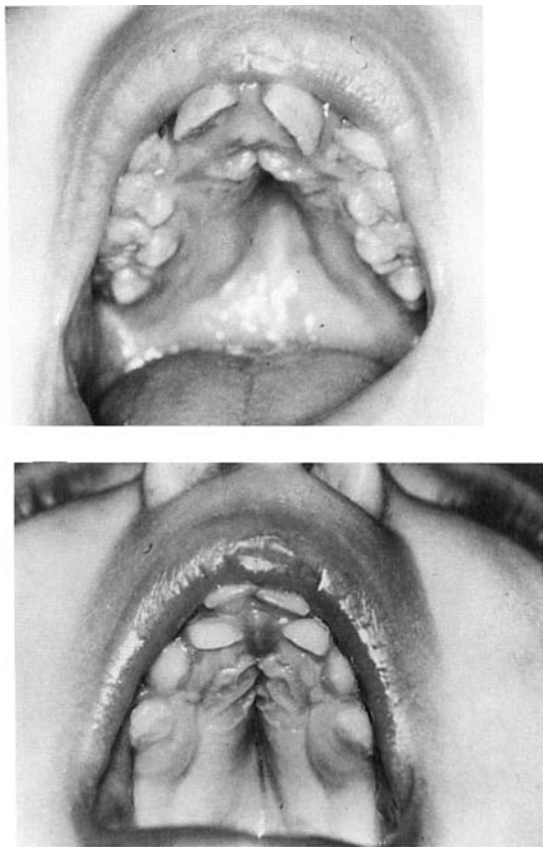


Fig. 6. The palate in BTHS appears highly arched, possibly secondary to broad alveolar processes. Teeth tend to be irregular and crowded: **a:** 8-year-old girl and **b:** 3-year-old girl.

distal phalanx (Fig. 8a), at times a distal notch; however, I have never seen a complete duplication of the phalanges of the thumb in BTHS. Radial angulation of the distal phalanx on the proximal phalanx (Fig. 7b) occurred in one or both thumbs in 48% of 451 cases. No thumb showed ulnar angulation. The angulation was usually secondary to the proximal phalanx having a trapezoid or triangular delta appearance (Fig. 8b). The epiphysis of the proximal phalanx ran longitudinally instead of transversely and bracketed the diaphysis on the radial side. In 75%, the radial angulation was bilateral. When unilateral, the right thumb was affected in 73%. The angulated thumb may be hyperextensible, but with somewhat limited functional abilities, particularly opposition and grasp.

Other fingers tended to have somewhat broad, short, or tufted terminal phalanges (Fig. 7).

Fifty-three operations carried out on 35 thumbs of 20 patients were recently reviewed [Wood and Rubinstein, 1987]. Simple pinning, primary fusion, and simple capsulotomy did not appear to produce improvement. Careful surgery on the delta phalanx with opening wedge, closing wedge, or reverse wedge osteotomies and K-wire insertion produced good functional and cosmetic results. It was recommended that operation be performed at age one to 2 years. The operation of choice, because of relative technical simplicity, was a closing wedge osteotomy with a K-wire insertion, and a Z-plasty on the concave side to straighten the thumb. At age 10 years further straightening could be done by fusing the metacarpophalangeal joint. Debulking of soft tissue and resection of bone could also be considered at that time.

Broadening of the hallux was often less obvious since the range of normal variation is even greater. When

TABLE V. Frequency of Skeletal Findings in BTHS

Finding	Present (%)	Absent	Not stated
Thumbs and first toes, broad terminal phalanges[a]	569 (100)	0	2
Thumbs, angulation deformity with abnormal shape of proximal phalanx	216 (48)	235	120
First toes, angulation deformity with abnormal shape proximal phalanx or first metatarsal	80 (23)	264	227
First toe, proximal phalanx duplicated	35 (12)	251	285
First toe, distal phalanx duplicated	48 (16)	244	279
Fifth finger clinodactyly	158 (49)	167	246
Toes, overlapping	150 (45)	186	235
Other fingers, broad terminal phalanges[a]	280 (73)	106	185
Pelvic anomalies: flat acetabular angles, flaring of ilia, notch in ischia	99 (61)	64	408
Gait, stiff[a]	148 (87)	23	400
Hypotonia, lax ligaments, hyperextensible joints[a]	216 (70)	94	261
Vertebral anomalies: spina bifida, kyphosis, lordosis, scoliosis	149 (63)	86	336
Sternal or rib anomalies: premature fusion, simian sternum, pectus excavatum or carinatum, forked ribs, cervical rib, fusion of ribs 1 and 2	198 (62)	122	251

[a] Occurs in 2/3 or more of cases in which finding is recorded.

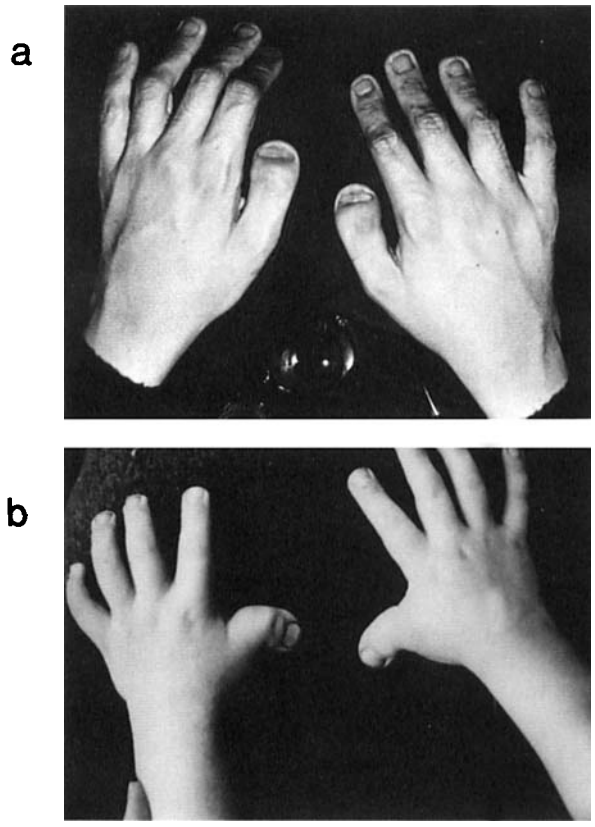


Fig. 7. Hands of individuals with BTHS. **a:** A 29-year-old man. The distal phalanx of the thumb is broad, short, and flat. The thumbnail also appears broad, short, and flat. The distal phalanges of the other digits also appear to be broad. **b:** A 2-year-old boy. The thumbs are radially angulated with the distal phalanx broad and short. Other fingertips also appear to be broad. There appears to be clinodactyly of the fifth digit bilaterally.

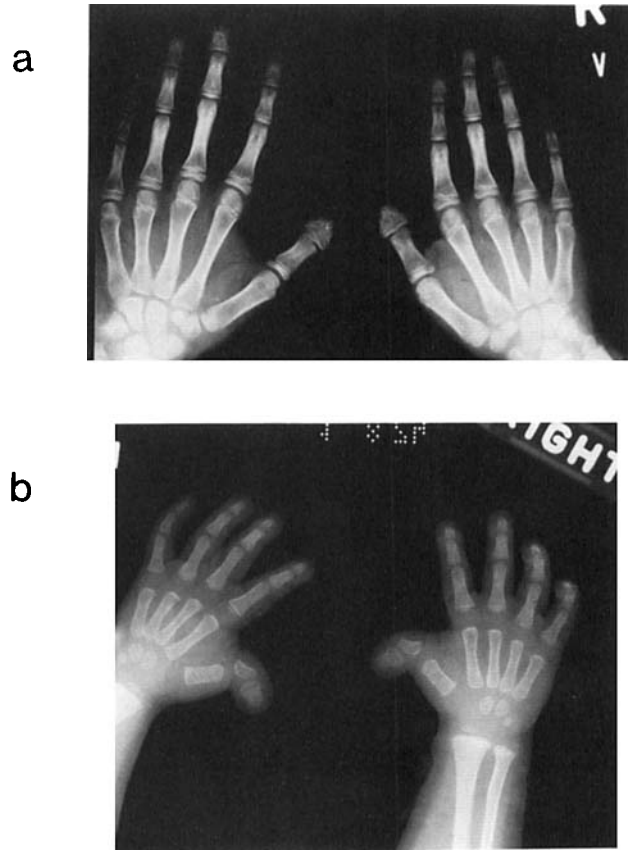


Fig. 8. Radiographs of the hands of individuals with BTHS. **a:** Hands of an 11-year-old girl. The distal phalanges of the thumbs are short and broad with a hole present on the left. **b:** Hands of a 2-year-old boy. The distal phalanges of both thumbs are radially deviated in relation to the deformed asymmetric delta-shaped proximal phalanges. There appears to be slight clinodactyly of the 5th digits bilaterally.

pronounced the hallux was wide, flat, or fan-shaped (Fig. 9). As in the thumb, only the distal phalanx might be enlarged; however, in other cases the whole ray appeared involved. Nail abnormalities often reflected underlying polydactyly (Fig. 9c).

Angulation deformity of the hallux occurred in 23% of 344 cases (Table V) and could be either in a medial (Figs. 9a, 10b,c) or lateral (Fig. 9b) direction, with or without a delta phalanx, and at the interphalangeal (Fig. 10b) or metatarsophalangeal (Fig. 10c) joint. A delta-shaped phalanx occurred most commonly in the proximal phalanx of the hallux (Fig. 10b), next in the metatarsal (Fig. 10c); and least commonly in the distal phalanx. Delta phalanges were bilateral in 53%.

When the proximal phalanx of the metatarsal of the hallux had a delta deformity, there was often polydactyly in the ray (Fig. 11; Table V). Polydactyly was reported in the distal phalanx in 16% (Fig. 11a,c), in the proximal phalanx in 12% (Fig. 11c) and only once in the metatarsal. Combined proximal and distal polydactyly occurred in about 20 cases (Fig. 11c), and in 62% polydactyly was bilateral. In addition, fifth toe polydactyly was reported in 24 cases.

Anomalies of the pelvis (Table V) included decreased acetabular angles, flare of the ilia, or a notch in the ischia [Taybi, 1968]. In 5 cases, there was the appearance of Legg-Calvé-Perthes disease [Coignet et al., 1969; Lahlou and Carrier, 1971]. A stiff gait was commented on in 87% (Table V).

Thirty-one fractures were recorded in 21 individuals with BTHS. In addition, 5 individuals were described as having a wide separation of the symphysis pubis.

Hypotonia, lax ligaments, and hyperextensible joints were recorded in 70% (Table V); however, deep tendon reflexes were hyperactive in 53%. In 15 individuals, there was dislocation or limitation of movement of the elbow. In 15 individuals there were anomalies and/or dislocation of the patella [Lamy et al., 1967; Herrmann and Opitz, 1969; Rohlfing et al., 1971; Rett et al., 1969], at times leading to loss of ambulation. In 18 individuals, there were anomalies of C1 and C2, including unfused posterior arches, and, less commonly, odontoid hypoplasia. In one 7-year-old boy, there was radiographic evidence of atlanto-axial instability and surgery was attempted.

Vertebral anomalies, including spina bifida, ky-

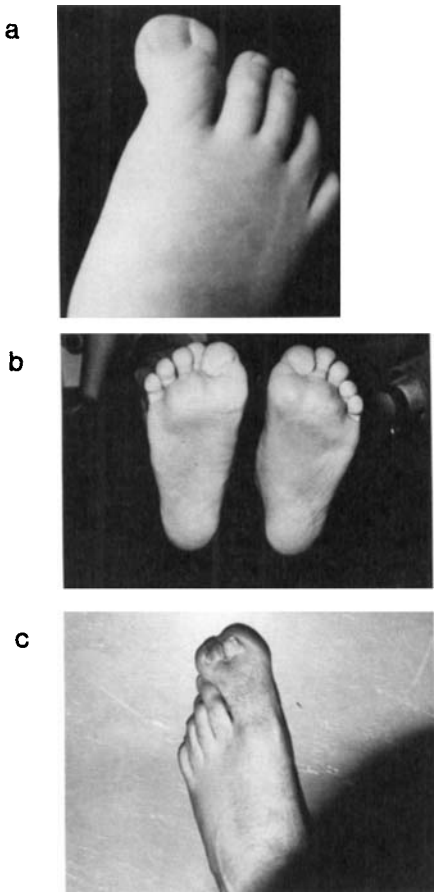


Fig. 9. Feet in individuals with BTHS. **a:** The distal phalanx of the right hallux of a 2-year-old boy is broad and is displaced and deviated medially. There is a tendency for the nail to be ingrown. There is slight overlap of the second and third toes over the fourth and clinodactyly of the fifth (see 10c). **b:** Plantar surface of foot of an 11-year-old girl. The distal phalanges of the halluces are broad, fan-shaped and, in this patient, laterally deviated. There is a deep plantar crease between the first and second toes. **c:** The left hallux of a 29-year-old man is broad and appears almost bifid with a notch at the tip. The nail is bifid.

phosis, scoliosis, and lordosis, were recorded in 63% (Table V) and 4 individuals had associated myelomeningocele. Sternal and/or rib anomalies occurred in 62% (Table V).

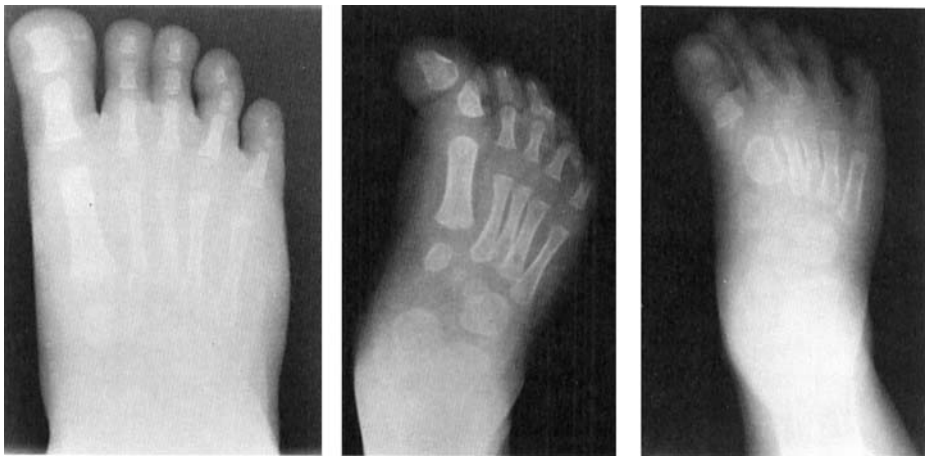
Heart disease, usually congenital heart defects with a wide variety of lesions, was recorded in 34% of 287 individuals [Rubinstein, 1971; Sautarel et al., 1978] (Table VI). Lesions included patent ductus anteriosus in 30 individuals, ventricular septal defect in 9, atrial septal defect in 11, various forms of coarctation of aorta in 9, and a wide variety of complex congenital heart abnormalities. Cor pulmonale, conduction defects, and cardiomyopathy have also been recorded. Stirt [1981, 1982] stresses the risk of cardiac arrhythmias with the use of cardioactive drugs during anesthesia (e.g., atropine, neostigmine, and succinylcholine).

Renal anomalies, urinary tract infections, and 4 individuals with nephrosis [Brandner and Saur, 1972; Tanphaichitr et al., 1979] have all been recorded (Table VI). Incomplete or delayed descent of testes was reported in 82% of 267 males (Table VI).

Cutaneous findings (Table VII) have included unusual dermatoglyphic patterns, supernumerary nipples, simian crease, deep plantar crease between the first and second toes, hirsutism, flat capillary hemangiomata on the forehead or elsewhere, ingrown nails/paronychiae, occasionally prominent cone-like pads on the ball of the fingers, and keloids and/or hypertrophic scars [Goodfellow et al., 1980; Kurwa, 1978; Selmanowitz and Stiller, 1981]. In addition to the keloids, there were 17 individuals with BTHS and neoplasms. Keloids and neoplasms in BTHS will be described in a separate report.

Abnormalities of glucose metabolism from hypoglycemia to frank diabetes have been recorded in 10 individuals with BTHS [Rohlfing et al., 1971; Bartok et al., 1968; Völcker and Haase, 1975].

The cause of BTHS remains obscure. In this series of 571 individuals, as shown in Table VIII, concordance for BTHS with some phenotypic variance has been reported in 4 probable monozygotic twins [Pfeiffer, 1968; Bar-



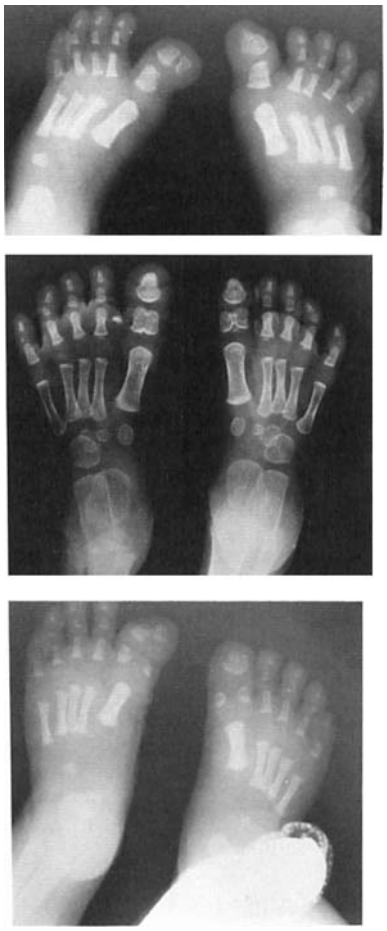


Fig. 11. Radiographs of feet of individuals with BTHS. **a:** Both halluces are enlarged in a 2-day-old girl. There is duplication of the distal phalanx of the left great toe with the medial portion about one-half the size of the other portion. Distal phalanx of right hallux is enlarged with a hole in the center and a notch at both ends. Proximal phalanges of halluces are wide and slightly short with distal surfaces that slope slightly medially. **b:** Distal phalanges of the halluces in a 2½-year-old boy are short and broad with a possible hole on the right. There is a tendency to a bifid proximal phalanx on the left side with a notch on the proximal and distal ends and an almost complete bifid phalanx (butterfly shape) on the right. **c:** A newborn girl with proximal phalanges of halluces duplicated, delta in shape and with apices of each duplicated part facing each other, the lateral segment being larger than the medial. The distal phalanx of the right hallux is short and broad with a hole in the middle and a notch at each end. Distal phalanx of left hallux shows complete duplication with a soft tissue indentation (clinically nail was also bifid).

Fig. 10. Radiographs of feet of individuals with BTHS. **a:** Right foot of 3-year-old girl with broad distal phalanx of hallux with slight notch proximally. **b:** The distal phalanx of the right hallux in a 2-year-old boy is abnormally broad, displaced, and deviated medially in relation to the proximal phalanx which is stunted, deformed, and delta-shaped. **c:** Right first metatarsal of an 18-month-old girl is short, broad, and trapezoidal, almost delta-shaped with medial deviation of the phalanges of the hallux at the metatarsophalangeal joint. Proximal phalanx of hallux is slightly short and the distal phalanx is short and broad.

aitser and Preece, 1983] and 2 same-sexed twins [Kroth, 1966; Buchinger and Ströder, 1973; Holthusen and Panteliadis, 1971]. Discordance for BTHS in probable monozygotic twins has been reported in one case [Kajii et al., 1981]. A 13-year-old girl with BTHS was said to have had a twin who did not survive; however, it was not known whether the twins were concordant, monozygotic, or same-sexed [Sakurai et al., 1966].

Gorlin et al. [1976] refer to having seen concordant female identical twins; however, since details could not be secured, this pair of twins is not included in this series. Four other twin pairs were reported, 2 monozygotic and 2 "like-sexed," and one of these pairs was said to be concordant for BTHS but 3 were said to be discordant [Schinzel et al., 1979]. Since details of evidence for BTHS or zygosity could not be obtained in these cases, they are not included in this series.

Discordance for BTHS in same-sexed twins, probably dizygotic, was noted in 5 cases [Herrmann and Opitz, 1969; Kubota et al., 1972]. Discordance in unlike sexed twins was reported in 4 instances, and discordance was reported in one of alleged non-identical triplets.

Affected sibs, other than twins, with BTHS were reported in 7 families, but only in 3 to 4 instances was the diagnosis even likely [Johnson, 1966; Der Kaloustian et al., 1972; Hayem et al., 1970]. In one of the 4 families (Der Kaloustian et al., 1972], the diagnosis of BTHS in the sibs has recently been questioned by the author of the original article. In another of these 4 families, the affected sibs had 2 different fathers, one of European, the other of Indian extraction.

In another family, there was considerable question about the alleged involvement of the older brother of the proband [Levy-Leblond et al., 1969]. In 2 other families, there was question about the diagnosis of BTHS in both the proband and the sib [Takeuchi, 1966].

Four additional families were not tallied in this series of 571 individuals, because data were incomplete. In one family reported by Kistenmacher and Punnett [1984], an uncle and nephew were said to have BTHS. In a family reported by Cotsirilos et al. [1987], 2 sibs and the mother were thought to have BTHS based on a dominant genetic pattern. An article by Gillies and Rousounis [1985] reported a family with an affected uncle and nephew, and another family with 2 affected sibs.

Consanguinity was reported in 5 families [Verma, 1970; Der Kaloustian et al., 1972; Jéliu and Saint-Rome, 1967; Padfield et al., 1968; Levy-Leblond et al., 1969]. In one of these families there were 2 affected sibs [Der Kaloustian et al., 1972]; however, as has been stated, the diagnosis in these sibs is now in question. In another, the proband was the result of incest between father and daughter [Padfield et al., 1968].

In one case, a proband alleged to have BTHS gave birth to a 7-month premature infant without malformation; however, the diagnosis in the proband was questionable [Rohmer et al., 1970].

Three hundred fourteen individuals with BTHS were studied cytogenetically. Depending on when the studies were conducted, these were either banded or unbanded. High-resolution prometaphase G-banding conducted in 6 cases in this series, and in 5 other cases, was consid-

TABLE VI. Frequency of Cardiovascular and Genitourinary Findings in BTHS

Finding	Present (%)	Absent	Not stated
Lung: azygous lobe or other abnormal lobation	33 (27)	90	448
Heart murmur	150 (39)	236	185
Heart disease, congenital or other	99 (34)	188	284
Testes, incomplete or delayed descent[a]	219 (82)	48	45
Kidney anomalies or disease	103 (52)	95	373

[a] Occurs in 2/3 or more of cases in which finding is recorded.

TABLE VII. Frequency of Cutaneous Findings in BTHS

Finding	Present (%)	Absent	Not stated
Nipples, supernumerary	39 (16)	207	325
Capillary hemangiomata, flat, on forehead, nape of neck, or back	192 (61)	122	257
Hirsutism[a]	268 (75)	87	216
Simian crease	152 (4%)	162	247
Deep plantar crease between 1st and 2nd toes	91 (56)	72	408

[a] Occurs in 2/3 or more of cases in which finding is recorded.

TABLE VIII. Familial Cases of Broad Thumb-Hallux Syndrome (BTHS)

Relationship & evidence of zygosity	Concordance	Age (years)	Sex	Race	Reference	Comments
Probable monozygotic (MZ) twins						
1. Single placenta blood groups & serum factors: 98% probability	+	1 1/4	M, M	W	Pfeiffer [1968]	Twin I: hyperthelia; twin II: metopic synostosis, natal teeth & cryptorchidism
2. Blood groups: more than 99% probability	+	8	F, F	W	Baraitser and Preece [1983]	Twin I: Patent ductus
3. 12 blood group systems identical	+	10 1/3	F, F	W	Baraitser and Preece [1983]	Twin I: 6th toe on rt. Pat cousin with Down Syndrome
4. Monochorionic diamniotic single placenta	+	3	M, M	W	—	Minor x-ray differences between twins
5. Both ARh+	+	7 5/6	M, M	W	Kroth [1966]; Buchinger and Stróder, [1973]	Originally diagnosed as deLange
6. Both ARh+, died before other tests of zygosity could be performed	+	3 days 26 days	F, F	W	Holthusen and Panteliadis, [1971]	Premature Twin I: d. at 3 days; twin II: d. at 26 days heart failure with patent ductus; minor phenotypic and x-ray differences
7. Blood groups, serum proteins, isoenzymes, HLA, earwax type, sequential Q and R band heteromorphism 99.9998% probability	−	4 3/4	M, M	O	Kajii et al. [1981]	Twin I: BTHS; twin II: normal
Twins of unknown zygosity						
1. —	?	13	F, ?	W	Sakurai et al. [1966]	Twin did not survive

(continued)

TABLE VIII. Familial Cases of Broad Thumb-Hallux Syndrome (BTHS) (*continued*)

Relationship & evidence of zygosity	Concordance	Age (years)	Sex	Race	Reference	Comments
Probable dizygotic (DZ) twins:						
1. Blood group differences	–	12	F, F	W	Herrmann and Optiz [1969]	Twin I: BTHS
2. Blood group differences	–	1 2/3	M, M	O	Kubota et al. [1972]	Twin II: BTHS
3. Blood group differences	–	11 1/3	M, M	W	—	One of twins with BTHS
4. Two placentas and blood group differences	–	4	M, M	W	—	Twin I: BTHS; twin II: has congenital aortic stenosis & ureteral reflux
5. Blood group differences	–	29	M, M	W	—	Twin I: BTHS; developed glomus tumor and seminoma
6. Unlike sex	–	17 2/3	M, F	B	—	12 pregnancies: 7 liveborn, 1 infant died, last pregnancy twins; twin II: BTHS (5 miscarriages)
7. Unlike sex	–	1 7/12	F, M	B	—	Twin I: d. congestive failure, post-repair atrial septal defect; severe pulmonary hypertension; twin II: normal brother; 4 yr-old brother with neuroblastoma
8. Unlike sex	–	2	F, M	W	—	Twin II: BTHS
9. Unlike sex	–	3	F, M	W	—	Twin II: BTHS
Triplets of unknown zygosity						
1. —	–	6	M, M, M	W	—	3rd triplet: BTHS
Sibs						
1. —	+	10/52, 3 1/2	M F	W	Johnson [1966]	
2. —	+?	3, 1 5/12	F F	W	Hayem et al. [1970]	Younger sib with less clear-cut findings
3. —	+	1 10/12, 10/12	F M	W	Der Kaloustian et al. [1972]	Minimal digital findings in both sibs; parents are first cousins; dx of BTHS now questioned by Der Kaloustian
4. —	+	15, 6 1/2	M M	W W	—— ——	Father of older sib of European extraction; father of younger sib of Indian extraction

* + = concordant; – = discordant; ? = unknown concordance; M = male; F = female; W = white; B = black; O = Oriental; D = died.

ered normal [Wulfsberg et al., 1983]; however, initial analysis of 2 patients raised the question of a small chromosome deletion in 15q [Wulfsberg et al., 1981, 1982]. Two cultures in this series were treated to induce breakage but no consistent breakage pattern was found.

Of the 314 individuals with BTHS studied cytogenetically, all but 15 were reported as "normal" (Table IX). Eight of the 15 had polymorphisms of heterochromatin [Rubinstein, 1969; Simpson, 1973; Juttnerová et al., 1977; deToni et al., 1982]. Two of the 15 were possible structural variants of "C" chromosomes Davison et al., 1967; Hayem et al., 1970]; however, these were both unbanded. There were 3 trisomies for an "F" or "G" chromosome [Van Gelderen et al., 1967; Bazacliu et al., 1973; Simpson, 1973], and of the 3, 2 were mosaics [Van Gelderen et al., 1967; Bazacliu et al., 1973]. There was one deletion of 10p or 12p in an unbanded preparation [Laurent et al., 1968] and there was one deletion in chromosome 1(46,XX,del[1][q?24]. Therefore, 10 of the 15 cytogenetic studies represented polymorphisms or variants leaving 5 with possible chromosome abnormalities.

DISCUSSION

The incidence and prevalence of BTHS in the general population are unknown. Reports of frequencies for institutionalized populations in the 1960s varied from 16 out of 4,838 patients (one in 300) in Ontario, Canada

TABLE IX. Three Hundred Fourteen Individuals With BTHS Studied Cytogenetically: Abnormal Cytogenetic Findings and Polymorphisms/Variants

Karyotype	Classification	Reference
46,XX/47,XX + der(20)(qter13.3,p11.2)	Mosaic trisomy	[Van Gelderen et al., 1967]
46,XX,Dph+[a]	Polymorphism	[Rubinstein, 1969]
46,XY,16qh+[b]	Polymorphism	[Padfield et al., 1968; Simpson, 1973]
47,XX +G or 47,XX,+del (14q)	Trisomy	[Simpson, 1973]
46,XX,?var(C)	Variant	[Davison et al., 1967]
46,XX,?var(C)	Variant	[Hayem et al., 1970]
46,XY, del (?10p or ?12p)	Deletion	[Laurent et al., 1968]
46,XY/47,XY+F/47,XY+G,?del(A)	Mosaic trisomy	[Bazacliu et al., 1973]
46,XY,Yqh+	Polymorphism	—
46,XX, del(1)(q?24)	Deletion	—
46,XY,17s+,16qh+	Polymorphism	—
46,XY,16qh−	Polymorphism	[Juttnervová et al., 1977]
46,XY,16qh+	Polymorphism	[de Toni et al., 1982]
46,XX,9qh+	Polymorphism	—
46,XY,9qh+	Polymorphism	—

[a] Same karyotype in patient's father.
[b] Same karyotype in patient's mother and 5 of his close but clinically normal relatives.

[Padfield et al., 1968], 3 out of 1600 (one in 500) at Harperbury Hospital, England [Berg et al., 1966], to 5 out of 3600 (one in 720) in California [Coffin, 1964]. A children's mental retardation evaluation clinic reported a frequency of 11 out of 2,937 (one in 267) in Cincinnati [Rubinstein, 1969]. More recent data (1970–1980) from a general genetic service in San Francisco identified 16 cases and indicated that it was one of the 25 most common multiple congenital anomaly syndromes seen in that setting [Hall, 1981].

This series of 571 BTHS cases represents an almost 30-year data collection, combining those cases that came to the Cincinnati Center for Developmental Disorders, those published by others, and those reported to the author through personal communication. An active effort was made to learn details of as many new cases of BTHS as possible by informing clinicians, centers, and parents' groups of this author's interest. An attempt was also made, with varying degrees of success, to obtain additional details, such as photographs and roentgenograms, on most published cases. Follow-up questionnaires were sent to a number of the families of individuals personally examined and periodic reports were received from a few of the families with whom we have corresponded; however, there has not yet been a systematic attempt to get long-term follow-up on this series.

Many of the cases diagnosed as BTHS were published in the early years after the 1963 report [Rubinstein and Taybi, 1963]. Published reports became less common since they understandably became "unacceptable for publication" unless there was some unique finding. Even the personal communications on recent cases became more limited to those with complex problems; however, additional cases were ascertained through relatively recently formed Irish, English, and American parent support groups.

Diagnosis of BTHS may be missed when the individual is being cared for by a physician specializing in one of the associated problems, such as heart disease or renal disease, and who may not be familiar with BTHS or where concern for a life-endangering problem properly outweighs concerns for syndrome diagnosis. The current philosophical trends away from "labeling" and "medical models" may also contribute to failure in diagnosing BTHS. The difficulty in making the diagnosis in other racial groups has already been mentioned. For all of these reasons, it would appear probable that our ascertainment of persons with BTHS is far from complete.

On the other hand, there is the risk of overdiagnosis. I probably accepted early published cases with less strict criteria than I have applied more recently.

In 1987, on a visit to one of the Rubinstein-Taybi syndrome support groups, I saw 25 individuals diagnosed as having BTHS in 21 families; however, I was able to agree with the diagnosis of BTHS in only 13 individuals. I had great concern about dealing with the families in which I could not confirm the diagnosis. It turned out that with all of them waiting together in the same playroom, most of the families of the other 12 individuals quickly recognized their children did not quite fit the BTHS gestalt and so informed me before I had to question the diagnosis.

It is of interest that Partington and Girard [1988] attempted a follow-up of the 17 patients reported in 1968 [Padfield et al., 1968] In 9 they thought that the diagnosis of BTHS was valid. The diagnosis was in doubt in 2 that could not be located and in 6 that were seen personally for follow-up. At that same meeting in Oakland, Der Kaloustian questioned the diagnosis of BTHS in the 2 affected sibs reported earlier [Der Kaloustian et al., 1972].

Over the years, many investigators have argued that less strict criteria be employed for the diagnosis of BTHS; I have pleaded to maintain the strict criteria—including broad thumbs and halluces and the facial phenotype, especially where unusual associations or familial cases are being reported. When a pathognomonic marker can be identified, I have no question that individuals with BTHS will be identified in which the currently required strict diagnostic criteria may be absent.

Through the collaboration of many professionals from around the world, and with the cooperation of families of individuals with the syndrome and their parent support groups, much has been learned about this rather common multiple congenital anomaly syndrome [Hall, 1981]. There is still much to be learned. The application of new technologies as they become available, the continued longitudinal follow-up of known cases, and the careful collection of clinical, photographic, and roentgenographic data on all suspected cases will assist in filling the gaps in our knowledge and will clarify the natural history and cause(s) of the broad thumb-hallux (Rubinstein-Taybi) syndrome.

ACKNOWLEDGMENTS

I wish to express my appreciation to all of the individuals who assisted in gathering this information and translating articles; to Drs. Silverman, Dorst, and Oestreich and other members of the Division of Radiology of the Children's Hospital Medical Center who reviewed the radiographs; to my secretary Mrs. Rose Bush who painstakingly kept track of this information and prepared this manuscript; to all of the families and professionals without whose cooperation these data could not have been gathered; and to my late wife, Thelma, who continually encouraged me in these efforts and to whom this paper is dedicated.

This project was supported by grant No. MCJ-000-912-23-0, awarded by the Bureau of Health Care Delivery and Assistance, Division of Maternal and Child Health, Public Health Service, DHHS, and grant No. 07DD0269/07, awarded by the Administration on Developmental Disabilities, OHDS, DHHS.

REFERENCES

Baraitser M, Preece MA (1983): The Rubinstein-Taybi syndrome: Occurrence in two sets of identical twins. Clin Genet 23:318–320.

Bartok WR, Reed WB, Fish C (1968): Rubinstein-Taybi syndrome. Cutis 4:1350–1353.

Bazacliu E, Tonceanu S, Carp G, Ghişoiu V, Roşca GH, Roşca S (1973): Sindrom Rubinstein-Taybi cu modificări de cariotip şi pneumopatie recidivantă. Ftiziologia 22:645–650.

Berg JM, Smith GF, Ridler MAC, Dutton G, Green EA, Richards BW (1966): On the association of broad thumbs and first toes with other physical peculiarities and mental retardation. J Ment Defic Res 10:204–220.

Brandner M, Saur G (1972): Generalisierte Dysplasie der Epiphysen und metaphysäre Exostosen beim Rubinstein-Taybi-Syndrom. Fortschr Rontgenstr 117:317–323.

Buchinger G, Ströder J (1973): Rubinstein-Taybi-Syndrome bei wahrscheinlich eineiigen Zwillingen und drei weiteren Kindern. Gleichzeitige Korrektur einer Fehldiagnose. Klin Padiatr 185:296–307.

Coffin GS (1964): Brachydactyly, peculiar facies and mental retardation. Am J Dis Child 108:351–359.

Coignet JP, Aubrespy P, Passeron PH, Sitruk S (1969): Le syndrome de Rubinstein-Taybi. Arch Fr Pediatr 26:815, 816.

Cotsirilos P, Taylor JC, Matalon R (1987): Dominant inheritance of a syndrome similar to Rubinstein-Taybi. Am J Med Genet 26:85–93.

Davison BCC, Ellis HL, Kuzemko JA, Roberts DF (1967): Mental retardation with facial abnormalities, broad thumbs and toes and unusual dermatoglyphics. Dev Med Child Neurol 9:588–593.

Der Kaloustian VM, Afifi AK, Sinno AA, Mire J (1972): The Rubinstein-Taybi syndrome: A clinical and muscle electron microscopic study. Am J Dis Child 124:897–902.

de Toni T, Cavaliere G, Cortese M, Gastaldi R, Carozzino L, Duillo MT (1982): La sindrome di Rubinstein-Taybi: Presentazione di due nuovi casi. Minerva Pediatr 34:765–770.

Filippi G (1969): Rubinstein-Taybi syndrome in a Negro. In Bergsma D (ed): "Proceedings Conference on Clinical Delineation of Birth Defects, Part 2, Malformation Syndromes." New York: For the National Foundation. BD:OAS V (2):208–210.

Fukunaga N, Suda S, Ebihara Y, Laovoravit N, Laovoravit M (1969): Rubinstein-Taybi's syndrome: A case report. Acta Pathol Jpn 19:501–510.

Gardner DG, Girgis SS (1979): Talon cusps: A dental anomaly in the Rubinstein-Taybi syndrome. Oral Surg Oral Med Oral Pathol 47:519–521.

Gillies DRN, Roussounis SH (1985): Rubinstein-Taybi syndrome: Further evidence of a genetic aetiology. Dev Med Child Neurol 27: 751–755.

Goodfellow A, Emmerson RW, Calvert HT (1980): Rubinstein-Taybi syndrome and spontaneous keloids. Clin Exp Dermatol 5:369–371.

Gorlin RJ, Pindborg JJ, Cohen MM, Jr (1976): "Syndromes of the Head and Neck," 2nd ed. New York: McGraw-Hill Book Co, pp 657–660.

Grunow JE (1982): Case report: Gastroesophageal reflux in Rubinstein-Taybi syndrome. J Pediatr Gastroenterol Nutr 1:273–274.

Hall BD (1981): The twenty-five most common multiple congenital anomaly syndromes. In Kaback MM (ed): "Genetic Issues in Pediatric and Obstetric Practice." Chicago: Year Book Medical Publisher, pp 141–150.

Hayem F, Boisse J, Rethore MO, Labrune M, Hambourg M, Mozziconacci P (1970): Le syndrome de Rubinstein-Taybi: Discussion des formes incompletes et familiales. Pediatrie 25:89–102.

Herrmann J, Opitz JM (1969): Dermatoglyphic studies in a Rubinstein-Taybi patient, her unaffected dizygous twin sister and other relatives. In Bergsma D (ed): "Proceedings Conference on Clinical Delineation of Birth Defects, Part 2, Malformation Syndromes." New York: For the National Foundation. BD:OAS V (2): 22–24.

Holthusen W, Panteliadis CHR (1971): Rubinstein-Taybi syndrome bei fruhgeborener (wahrscheinlich eineiigen) Zwillingen. Monatsschr Kinderheilkd 119:523–527.

Jéliu G, Saint-Rome G (1967): Le syndrome de Rubinstein-Taybi: À propos d'une observation. Union Med Can 96:22–29.

Johnson CF (1966): Broad thumbs and broad great toes with facial abnormalities and mental retardation. J Pediatr 68:942–951.

Juttnerová V, Žižka J, Chaloupka R (1977): Rubinsteinuv-Taybiuv syndrome u dvouléteho chlapce. Cesk Pediatr 32:156, 157.

Kajii T, Hagiwara K, Tsukahara M, Nakajima H, Fukuda Y (1981): Monozygotic twins discordant for Rubinstein-Taybi syndrome. J Med Genet 18:312–314.

Kinirons MJ (1983): Oral aspects of Rubinstein-Taybi syndrome. Br Dent J 154:46, 47.

Kistenmacher ML, Punnett HH (1984): Rubinstein-Taybi syndrome in uncle and nephew (abstract). Am J Hum Genet 36:59S.

Kroth H (1966): Cornelia de Lange-Syndrom I bei Zwillingen (Amsterdamer Degenerationstyp). Arch Kinderheilkd 173:273–283.

Kubota Y, Orita Y, Moriga T, Asaka A (1972): Rubinstein-Taybi syndrome in one of dizygotic twins (abstract). Teratology 6:111, 112.

Kurwa AR (1978): Rubinstein-Taybi syndrome and spontaneous keloids. Clin Exp Dermatol 4:251–254.

Lahlou B, Carrier C (1971): Ménométrorragies et bifidité utérine dans un cas du syndrome du "pouce en spatule" (Rubinstein et Taybi). Rev Int Pediatr 14:5–14.

Lamy M, Jammet ML, Ajjan N, Alibert L, Boulesteix J (1967): Le syndrome de Rubinstein-Taybi. Arch Fr Pediatr 24:472.

Laurent C, Nivelon A, Hartman E, Guerrier G (1968): Monosomie partielle d'un chromosome du groupe C: (Cp-). Ann Genet (Paris) 11:231–235.

Levy-Leblond E, D'Oelsnitz M, Vaillant JM, Maroteaux P (1969): Le syndrome de Rubinstein et Taybi: A propos de quatre observations. Arch Fr Pediatr 26:523–535.

Matsoukas J (1973): Fatherhood of the so-called Rubinstein-Taybi syndrome. Am J Dis Child 126:860.

Michail J, Matsoukas J, Theodorou S (1957): Pouce bot argue en forte abduction-extension et autres symptomes concomitants. Rev Chir Orthop 43:142–146.

Mourigan H, DeOrden MC, DeAmbrosoni NS, Bazzano H, Garófalo O (1975): Pulgares y dedos gordos anchos y cortos: Sindrome de Rubinstein y Taybi. Arch Pediatr Urug 46(2):117–125.

Neuhäuser G, Schulze H (1968): Das Rubinstein-Taybi-Syndrom: Klinische und pneumencephalographische Befunde. Kinderheilkd 103:90–108.

Padfield CJ, Partington MW, Simpson NE (1968): Rubinstein-Taybi syndrome. Arch Dis Child 43:94–101.

Partington MW, Girard K (1988): Follow-up of a group of patients labelled as having the Rubinstein-Taybi syndrome 22 years ago (abstract). 1988 David W. Smith Workshop on Malformations and Morphogenesis, Aug. 3–7, Mills College, Oakland, California, p 93.

Pfeiffer RA (1968): Rubinstein-Taybi-Syndrom bei wahrscheinlich eineiigen Zwillingen. Humangenetik 6:84–87.

Pogacar S, Nora NF (1970): Micrencephaly with partial agenesis of the corpus callosum in Rubinstein-Taybi syndrome (brachydactyly, facial abnormalities and mental retardation). In "Proceedings of the Sixth International Congress of Neuropathology, Paris, August 31–September 4, 1970." Paris: Masson et Cie, pp 1148, 1149.

Rett A, Kahlich-Koenner DM, Madl W (1969): Klinische und anthropologische Untersuchungen zum Rubinstein-Taybi-Syndrom. Wien Med Wochenschr 119:378–383.

Rohlfing B, Lewis K, Singleton EB (1971): Rubinstein-Taybi syndrome: Report of an unusual case. Am J Dis Child 121:71–74.

Rohmer F, Collard M, Bapst J, Micheletti G (1970): Encéphalopathies infantiles et dysmorphies complexes: Un cas de syndrome de Rubinstein-Taybi. Rev Otoneuroophtalmol 42:306–312.

Rubinstein JH (1969): The broad thumbs syndrome: Progress report 1968. In Bergsma D (ed): "Proceedings Conference on Clinical Delineation of Birth Defects, Part 2, Malformation Syndromes." New York: For the National Foundation. BD:OAS V (2): 25–41.

Rubinstein JH (1971): Broad thumb-hallux syndrome. In Swoboda W, Stur O (eds): "'Syndromes' Proceedings of the International Congress of Pediatrics, Vienna, Austria, August 29–September 4, 1971". Vienna: Verlag der Wiener Medizinischen Akademie, pp 471–476.

Rubinstein JH, Taybi H (1963): Broad thumbs and toes and facial abnormalities: A possible mental retardation syndrome. Am J Dis Child 105:588–608.

Sakurai EH, Mitchell DF, Holmes LA (1966): Some craniofacial dysostoses: (Pierre) Robin's syndrome, Treacher Collins' syndrome, and a digito-facial-mental retardation syndrome: Report of 3 cases. J Oral Med 21:44–46.

Sautarel M, Choussat A, Sandler B, Bui-Authier F, Guiter F, Sehabiague J, Abadie D (1978): Syndrome de Rubinstein-Taybi associé a une triade de Fallot: A propos d'une observation: Review des complications cardiaques de la maladie. Pediatrie 33:593–598.

Schinzel AAGL, Smith DW, Miller JR (1979): Monozygotic twinning and structural defects. J Pediatr 95:921–930.

Selmanowitz VJ, Stiller MJ (1981): Rubinstein-Taybi syndrome: Cutaneous manifestations and colossal keloids. Arch Dermatol 117:504–506.

Simpson NE (1973): The Rubinstein-Taybi syndrome: Chromosomal studies. Am J Hum Genet 25:230–236.

Sinnette C, Odeku EL (1968): Rubinstein-Taybi syndrome: The first case in an African child and the first case recognized at birth. Clin Pediatr 7:488–492.

Stirt JA (1981): Anesthetic problems in Rubinstein-Taybi syndrome. Anesth Analg 60:534–536.

Stirt JA (1982): Succinylcholine in Rubinstein-Taybi syndrome. Anesthesiology 57:429.

Takeuchi M (1966): Rubinstein's syndrome in two siblings. Gunma J Med Sci 15:17–22.

Tanphaichitr P, Mekanandha V, Kotchbhakdi N (1979): A case of Rubinstein-Taybi syndrome associated with nephrotic syndrome. J Med Assoc Thai 62:44–46.

Taybi H (1968): Broad thumbs and great toes, facial abnormalities and mental retardation syndrome. In Richards BW (ed): "Proceedings of the First Congress of the International Association for the Scientific Study of Mental Deficiency, Montpelier, France, September 12–20, 1967." Surrey, England: Michael Jackson Publishing Co. Ltd., pp 596–599.

True CW, Rubinstein JH (1968): Pathological findings in a case of the Rubinstein-Taybi syndrome. In Richards DW (ed): "Proceedings of the First Congress of the International Association for the Scientific Study of Mental Deficiency, Montpelier, France, September 12–20, 1967." Surrey, England: Michael Jackson Publishing Co. Ltd., pp 613–614.

Van Gelderen HH, Schaberg A, Gaillard JLJ (1967): Een onderzoek naar chromosomale Afwijkingen bij Zwakzinnige, niet-Mongoloide Kinderen. Maandschr Kindergeneeskd 35:141–151.

Verma IC (1970): Rubinstein-Taybi syndrome: Case report. Indian Pediatr 7:672–674.

Völcker HE, Haase W (1975): Augensymptomatik beim Rubinstein-Taybi-Syndrom. Klin Monatsbl Augenheilkd 167:478–483.

Wood VE, Rubinstein JH (1987): Surgical treatment of the thumb in the Rubinstein-Taybi syndrome. J Hand Surg [Br] 12:166–172.

Wulfsberg EA, Klisak IJ, Sparkes RS (1981): Chromosome 15q interstitial deletions in the Rubinstein-Taybi syndrome (abstract). Am J Hum Genet 33:127A.

Wulfsberg EA, Klisak IJ, Sparkes RS (1982): Possible chromosome deletion of 15q in the Rubinstein-Taybi syndrome (abstract). Clin Res 30:120A.

Wulfsberg EA, Klisak IJ, Sparkes RS (1983): High resolution chromosome banding in the Rubinstein-Taybi syndrome. Clin Genet 23:35–37.

Ziring PR, Weiss DI, Cooper LZ (1974): The association of congenital glaucoma with the Rubinstein-Taybi syndrome. J Pediatr Opthalmol 11:203–206.