American Journal of Medical Genetics 32:169-173 (1989)

New Syndrome

Growth Hormone Deficiency, Wormian Bones, Dextrocardia, Brachycamptodactyly, and Other Midline Defects

Robert F. Stratton and Mark W. Parker

Department of Pediatrics, Wilford Hall United States Air Force Medical Center, Lackland Air Force Base, Texas

We report on a 17-month-old boy with Wormian bones, short stature, growth hormone deficiency, developmental delay, brachycamptodactyly, dextrocardia, cryptorchidism, midshaft hypospadias, hypoplastic left kidney, and imperforate anus. This unique combination of abnormalities has not been reported previously.

KEY WORDS: **brachydactyly, camptodactyly, hypospadias, cryptorchidism, dextrocardia, imperforate anus, growth hormone deficiency**

INTRODUCTION

Hypospadias has been reported to occur with other midline defects. We report on a child with a variety of midline defects who also had brachycamptodactyly, Wormian bones, and isolated growth hormone deficiency, constituting what we feel is a new syndrome.

CLINICAL REPORT

A 17-month-old boy was referred for evaluation of short stature. He was the second born to healthy nonconsanguineous parents. The family history was unremarkable except for a maternal first cousin with hypospadias. The mother smoked one pack of cigarettes per day and occasionally drank alcohol. She had an upper respiratory infection at 5 months gestation, and several days of a febrile gastroenteritis at 7 months. The patient was born by repeat cesarean section at 39 weeks. Birth weight was 1956 g (−4 SD) and length was 45.7 cm (10th centile). A low imperforate anus was repaired neonatally. Additional defects were a penile hypospadias, bilateral cryptorchidism, and an abnormal cardiac contour on chest film. The phallus was not considered small. Chromosomes were normal 46,XY. He was initially hypertonic with truncal extension, which has improved with time. He has been healthy except for repeated middle ear infections resulting in the insertion of tympanostomy tubes at age 12 months. Within 2 weeks of surgery he began sitting without support and crawling. At 13 months he was pulling to stand and saying "mama." Shortly thereafter he was cruising, and by 15 months he walked alone.

At a physical examination at 17 months the patient was measured at a length of 68 cm (−5 SD, and height-age of 7 months) and weighed 6.85 kg (−4 SD). The head was high anteriorly and sloped to a low occiput (Fig. 1). Occipto frontal circumference (OFC) was 45.5 cm (3rd centile). The palpebral fissures sloped downward. The eyelashes were dense, but in a single row. Inner canthal distance was 2.5 cm (50th centile) and outer canthal distance was 7.2 cm (25th centile). The ears were normally shaped and 5 cm long (50th centile); the right ear was apparently low-set and posteriorly angulated. The nasal bridge was high and wide, with a wide tip, small alae, and a very short columella. The philtrum was relatively smooth and the vermillion border was thin. The palate was high with a wide alveolar ridge and single midline maxillary incisor, although there was a midline maxillary frenulum. The jaw was slightly retruded and lay in the general line of a posteriorly sloping facial plane.

The chest had a greater anterior-posterior (AP) than transverse diameter. There was a 1 cm unbilical defect. The phallus was uncircumcised, and there was a ventral midshaft opening and bilateral cryptorchidism. The anus appeared normally placed. There was no limitation of

Received for publication February 29, 1988; revision received July 28, 1988.

The views expressed herein are those of the authors and are not necessarily the views of the United States Air Force or Department of Defense.

Address reprint requests to Col. Robert F. Stratton, Department of Pediatrics, Wilford Hall USAF Medical Center, Lackland AFB, TX 78236-5300.

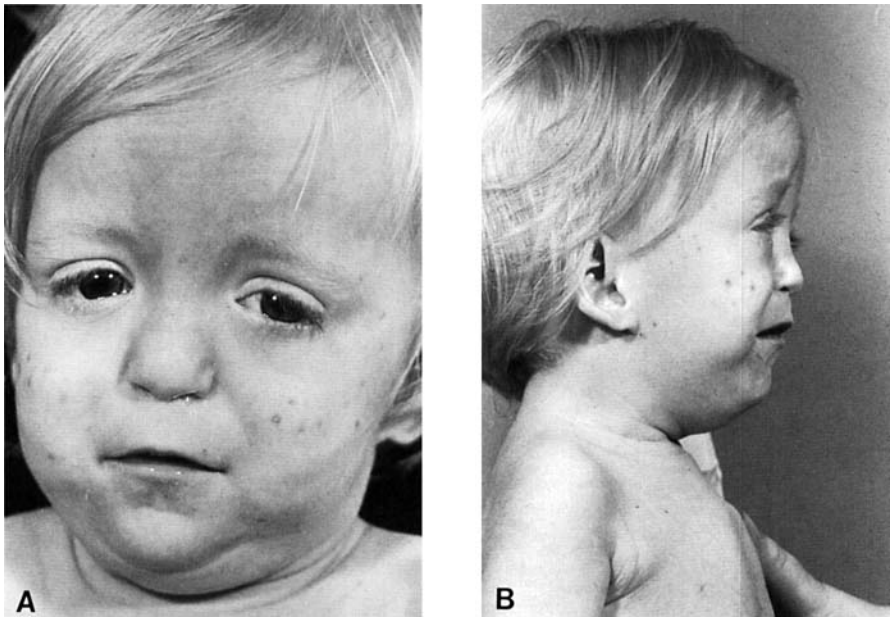

Fig. 1. Propositus.

any joint motion except in the hands. Total hand length was 7.2 cm (3rd centile), while middle finger length was only 2.4 cm (−5 1/2 SD). All fingers were distally tapered and had fixed flexion contractures (Fig. 2). Fingertip dermatoglyphics included ulnar loops on right 2 and 5 and left 1, with whorls on all others. Palmar creases were normal and axial triradii were in the T position. The feet measured 9.3 cm (< 3rd centile) with short first toes. There was no wrinkling or pigmentary change of the skin.

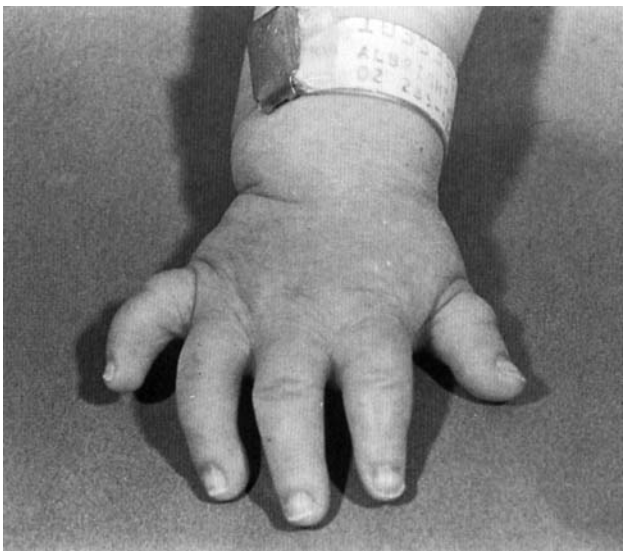

Fig. 2. Short camptodactylous fingers.

Comprehensive developmental assessment showed mild global delays with the following developmental quotients: gross motor, 88; fine motor, 59; selfhelp, 82; receptive language, 71; expressive language, 71; and problem solving, 71. Some delay in fine motor skills was attributed to the flexion contractures. There was also some concern that lack of exposure to age appropriate developmental toys may have influenced his performance.

Roentgenograms showed multiple Wormian bones with open sutures (Fig. 3). There was a single midline maxillary incisor with 2 unerupted lateral primary incisors and 2 permanent central incisor buds. The middle and distal phalanges were small (Fig. 4). Bone age was 1 1/2 year [Gruelich and Pyle, 1959]. The remainder of the skeleton was normal. Enhanced cranial CT scan with sellar cuts was normal. ECG showed left axis deviation, and echocardiography showed rightward rotation of the heart with normally oriented ventricles and a patent ductus arteriosus. Intravenous pyelogram (IVP) showed a small (52 mm length vs. 70 mm on the right) and poorly functioning left kidney. Cystourethrogram failed to show a patent urethra distal to the ventral opening. Serum electrolyte, glucose, calcium, phosphorus, magnesium, uric acid, total protein and albumin levels, and complete blood count were normal. BUN remained elevated around 30 with normal creatinine on 2 studies. SGOT was slightly elevated at 53 (nl 10–42) with normal SGPT, gamma GT, and lactic dehydrogenase (LDH). Total T4 and thyroid stimulating hormone (TSH) levels were normal. AM cortisol level was normal, with failure to secrete growth hormone on L-dopa/arginine stimulation according to the method of Weldon et al. [1975].

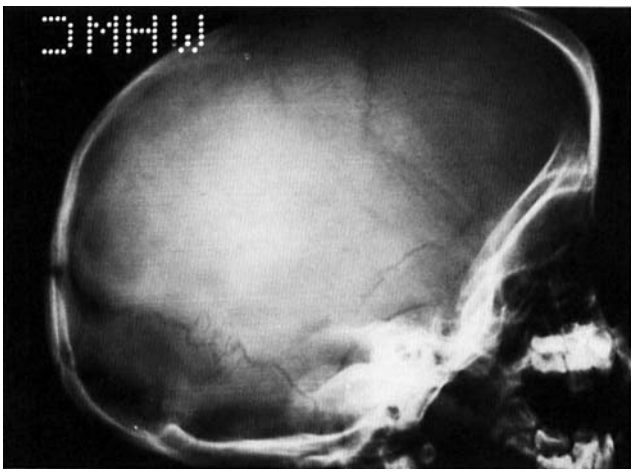

Fig. 3. Hand. Note Wormian bones in lambdoidal sutures and parietal bones.

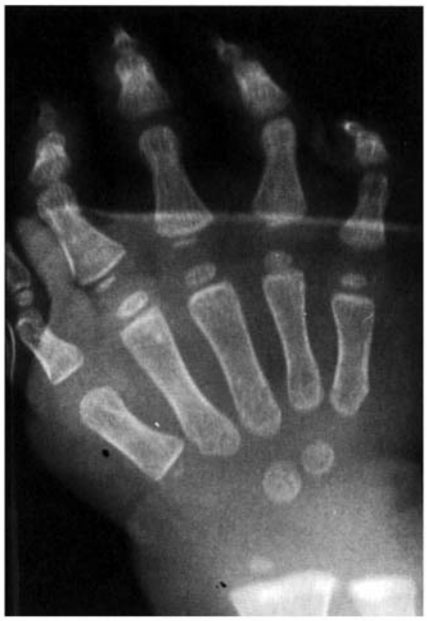

Fig. 4. Radiograph of right hand. Note flexion of interphalangeal joints including thumb.

DISCUSSION

This child presents a unique combination of abnormal skull growth with unusual face, growth hormone deficiency, developmental delay, brachycamptodactyly, and several midline defects.

Wormian bones can be seen in several entities, remembered with the mnemonic ICHOP. The first is idiopathic, with two or more bones being seen in a small percentage of the general population. Cleidocranial dysostosis was considered because of the patient's narrow shoulders, but the normal radiographic appearance of the clavicles and pelvis along with other defects present make both the classic form and the similar-appearing cases described by Goodman et al. [1975] and Yunis and Varón [1980] unlikely. Hypothyroidism is excluded because the patient's thyroid function is normal. Osteogenesis imperfects (OI) occurs in several clinical forms with varying severity of fractures and scleral hues [Byers and Bonadio, 1985]. The sibs with OI reported by Heide [1981] had brachycamptodactyly but were also blind and lacked midline defects. Also included in the OI group is Grant syndrome [Maclean et al., 1986], a combination of abnormalities that also includes blue sclerae, abnormal shoulder function, and bowed limbs. Our patient does not appear to fit into this group of diorders. Pynknodysostosis was also considered because of the growth failure, but lack of osteosclerosis excludes this diagnosis.

In arthro-dento-osteo dysplasia (Hajdu–Cheney syndrome), persistent Wormian bones may also be seen [Herrmann et al., 1973], but our patient had no hyperextensible joints or osteolytic lesions.

Neuhäuser et al. [1976] reported a series of patients with short stature and abnormal skull growth from premature fusion of the posterior sutures (Craniofacial dyssynostosis). The resultant increased frontal growth gave a characteristic high broad forehead with downward slope of the palpebral fissures. The nose was also peculiar in some of their patients, with a very short nasal septum and small nasal alae similar to our patient. None of the other subjects had other defects similar to our patient.

When the cardiac image is shifted rightward, one generally thinks of "dextrocardia," a term that implies that the ventricular mass is in the right chest [Garson, 1983]. This occurs in 3 conditions: mirror-image dextrocardia, when the anatomic right ventricle is to the left and anterior; ventricular inversion, when the ventricles are malposed, giving left axis deviation like that seen on our patient's ECG; and dextroratation, when the ventricles are normally positioned, and the heart is shifted and rotated to varying degrees into the right chest. Since the echocardiagram showed normal ventricle position, our patient had the third entity, dextrorotation. This condition is less likely to be associated with abnormal cardiac loop formation, and the unusually narrow chest seen in our patient may have contributed to this finding.

Hypospadias occurs in 2–8.2/1000 liveborn males [Leung et al., 1985]. A complicated interplay of tissue growth and induction and hormone influence is needed for proper urethral development between the 8th and 12th gestational weeks [Bellinger, 1981]. This defect may occur as an isolated defect with both autosomal recessive [Frydman et al., 1985] and autosomal dominant inheritance [Page, 1979; Lowry and Kilman, 1976]. Leung et al. [1985] found that 20% of their 264 hypospadias patients had at least one additional birth defect. Nine had bilateral cryptorchidism, 4 had imperforate anus, and 35, 14, and 28 had other nonspecified defects of the limbs, urinary tract, and cardiovascular system, respectively.

Syndromal hypospadias is seen in combination with hypertelorism in the G and the BBB syndrome(s). Some researchers think these can be differentiated in later life by facial differences [Cordero and Holmes, 1978].

Our patient did not resemble patients with either syndrome. In their review of the G and BBB syndromes, Funderburk and Stewart [1978] found prominent forehead (2/12 vs. 2/15) and imperforate anus (3/19 vs. 2/15) to be equally distributed between the two syndromes. Antimongoloid slant of palpebral fissures (3/15), short hands (1/15), cryptorchidism (6/15 vs. 1/18), and cardiovascular anomalies (3/14 vs. 1/5) were seen more frequently in the BBB syndrome. Our patient's mother had relative hypotelorism, making inheritance of either syndrome through her an unlikely explanation for the occurrence of hypospadias in her son and nephew.

Our patient had several midline field defects, as defined by Opitz and Gilbert [1982]. This combination of defects can be seen in the VACTERL association. In 90 cases of imperforate anus, Filippi [1972] found 4 cases of cryptorchidism, 3 of "atrophy" of a kidney, and 6 of hypospadias. He listed no cases of camptodactyly or brachydactyly. Khoury et al. [1983] found 4 cases of dextrocardia among their VACTERL patients. We do not know what form of dextrocardia was seen or if this was isolated or in combination with other cardiac defects. Hersh et al. [1986] reported a child with the VACTERL-like Townes syndrome who was the first with that syndrome to have hypospadias and congenital heart disease. This syndrome includes abnormally shaped ears and radial defects not seen in our patient.

Camptodactyly is seen in several syndromes, as summarized elsewhere [Welch and Temtamy, 1966; Goodman et al., 1972; Gordon et al., 1969; Poznanski, 1984]. Grosse [1974] reported a family with the Rabenhorst syndrome. The family reported by Say et al. [1976] had triphalangeal thumbs and patellar dislocation not seen in our patient. Cantú et al. [1980] added a unique family to the list of associations: the Guadalajara camptodactyly syndrome and later the Guadalajara II syndrome [Cantú et al., 1985]. None of these bear clinical resemblence to the condition seen in our patient. Hall et al. [1982] provided an extensive review of distal arthrogryposis. Other than short stature, there were no other similarities to our patient.

The relatives reported by Edwards and Gale [1972] with camptobrachydactyly had similar hand features, but only the presumed homozygous child (VI-8) had hypospadias. The sibs with W syndrome [Pallister et al., 1974] had less extensive camptodactyly, a high forehead and short philtrum and nasal septum similar to those of our patient, but also had other skeletal defects not seen in our patient. Patient 8 of Currarino and Waldman [1964] had bilateral 4 and 5 camptodactyly, ptosis, left ureteropelvic obstruction, and possible pituitary dwarfism. Their patient 12 had imperforate anus, club feet, hydrocephalus, and absent right pectoral muscle.

The association between midline facial defects and growth hormone deficiency is well known. Rappaport et al. [1977] reported 5 children with the association of growth hormone deficiency and single upper central incisor. Since absence of the midline maxillary frenulum may the the most subtle finding of the holoprosencephaly sequence, presence of a midline frenulum makes our patient's single tooth less likely to be associated with holoprosencephaly. Two premanent central incisor tooth buds and a normal cranial CT scan confirm this assumption.

In summary, we present a patient with several midline defects seen in the VACTERL association: craniofacial features of craniofacial dyssynostosis, brachycamptodactyly, Wormian bones, growth hormone deficiency, dextrocardia, and developmental delay. To our knowledge, a similar pattern of abnormalities has not been previously reported. He appears to have a new syndrome, but there is insufficient information to speculate on its mode of inheritance.

REFERENCES

Bellinger MF (1981): Embryology of the male external genitalia. Urol Clin N Am 8:375–382.

Byers PH, Bonadio JF (1985): The molecular basis of clinical heterogeneity in osteogenesis imperfecta: Mutations in type I collagen genes have different effects on collagen processing. In Lloyd J, Scriver CR (eds): "Metabolic Diseases in Pediatrics." London: Butterworths, pp 56–90.

Cantú JM, Garciá-Cruz D, Gil-Viera J, Nazará Z, Ramírez ML, Solé-Pujod MT, Sánchez-Corona J (1985): Guadalajara camptodactyly syndrome II. Clin Genet 28:54–60.

Cantú JM, Rivera H, Nazará Q, Hernández A, Garciá-Cruz D (1980): Guadalajara camptodactyly syndrome a distinct probably autosomal recessive syndrome. Clin Genet 18:153–159.

Cordero JF, Holmes LB (1978): Phenotypic overlap of the BBB and G syndromes. Am J Med Genet 2:145–152.

Currarino G, Waldman D (1964): Camptodactyly. Radiology 92:1312–1321.

Edwards JA, Gale RP (1972): Camptobrachydactyly: A new autosomal dominant trait with two probable homozygotes. Am J Hum Genet 24:464–474.

Filippi G (1972): The syndrome of polydactyly, imperforate anus and vertebral anomalies. In Bergsma D (ed): "The Clinical Delineation of Birth Defects Part XIII". Baltimore: Williams and Wilkins, for the National Foundation–March of Dimes. BD: OAS VIII(2):88–94.

Frydman M, Greiber C, Cohen HA (1985): Uncomplicated familial hypospadias: Evidence for autosomal recessive inheritance. Am J Med Genet 21:51–55.

Funderburk SJ, Stewart R (1978): The G and BBB syndrome: Case presentations, genetics and nosology. Am J Med Genet 2:131–144.

Garson A (1983): "The Electrocardiogram in Infants and Children: A Systemic Approach." Philadelphia: Lea & Febiger, pp 84–90.

Goodman RM, Katznelson MB, Manor E (1972): Camptodactyly: Occurrence in two new genetic syndromes and its relationship to other syndromes. J Med Genet 9:203–212.

Goodman RM, Tadmor R, Becker SA (1975): Evidence for an autosomal recessive form of cleidocranial dysostosis. Clin Genet 8:20–29.

Gordon H, Davies D, Berman M (1969): Camptodactyly, cleft palate, and club foot, a syndrome showing the autosomal-dominant pattern of inheritance. J Med Genet 6:266–274.

Grosse FR (1974): The Rabenhorst-syndrome, a cardio-acro-facial syndrome. Z Kinderheilk 117:109–114.

Greulich AA, Pyle SI (1959) "Radiologic Atlas of Skeletal Development of the Hand and Wrist." Stanford, CA: Stanford University Press.

Hall JG, Reed SD, Greene G (1982): The distal arthrogryposes: delineation of new entities-review and nosologic discussion. Am J Med Genet 11:185–239.

Heide T (1981): Ein Syndrom bestehend aus Osteogenesis imperfecta, Makrozephalus mit Schaltknöchen und prominenten Stirnhöckern, Brachytelphalangie, Gelenküberstreckbarkeit, kongenitaler Amaurose und Oligophrenie bei drei Geschwistern. Klin Padiatr 193:334–340.

Herrman J, Zugibe FT, Gilbert EF, Opitz JM (1973): Arthro-dento-osteo dysplasia (Hajdu–Cheney syndrome) Review of a genetic "acro-osteolysis" syndrome. Z Kinderheilk 114:93–110.

Hersh JH, Jaworski M, Solinger RE, Weisskopf B, Donat J (1986): Townes syndrome a distinct multiple malformation syndrome resembling VACTERL association. Clin Pediatr 25:100–102.

Khoury MJ, Cordero JF, Greenberg F, James LM, Erickson JD (1983): A population study of the VACTERL association: Evidence for its

etiologic heterogeneity. Pediatrics 71:815–820.

Leung TJ, Baird PA, McGillivray B (1985): Hypospadias in British Columbia. Am J Med Genet 21:39–48.

Lowry RB, Kilman MR (1976): Hypospadias in successive generations-possible dominant gene inheritance. Clin Genet 9:285–288.

Maclean JR, Lowry RB, Wood BJ (1986): The Grant syndrome: persistent Wormian bones, blue sclerae, mandibular hypoplasia, shallow glenoid fossae and campomelia—an autosomal dominant trait. Clin Genet 29:523–529.

Neuhäuser G, Kaveggia EG, Opitz JM (1976): Studies of malformation syndromes of man XXXIX: A craniosynostosis-carniofacial dysostosis syndrome with mental retardation and other malformations: "Craniofacial dyssynostosis." Europ J Pediatr 123:15–28.

Opitz JM, Gilbert EF (1982): CNS anomalies and the midline as a "developmental field." Am J Med Genet 12:443–455.

Page LA (1979): Inheritance of uncomplicated hypospadias. Pediatrics 63:788–790.

Pallister PD, Herrmann J, Spranger JW, Gorlin RJ, Langer LO, Opitz JM (1974): The W syndrome studies of malformation syndromes of man XXVIII. In Bergsma D (ed): "Malformation Syndromes." New York: Intercontinental Medical Book Corp., for the National Foundation—March of Dimes. BD:OAS X(7):51–59.

Poznanski AS (1984): "The Hand in Radiologic Diagnosis." Philadelphia: WB Saunders, pp 290–292.

Rappaport EB, Ultstrom RA, Gorlin RG, Lucky AW, Colle E, Miser J (1977): Solitary central incisor and short stature. J Pediatr 91:924–928.

Say B, Field E, Coldwell JG, Warnberg L, Atasu M (1976): Polydactyly with triphalangeal thumbs, brachydactyly, and camptodactyly, congenital dislocation of the patellas, short stature and borderline intelligence. In Bergsma D, Schimke RN (eds): "Cytogentics, Environment and Malformation Syndromes." New York: Alan R. Liss, Inc., for the National Foundation—March of Dimes. BD:OAS XII(5):279–286.

Welch JP, Temtamy SA (1966): Hereditary contractures of the fingers (camptodactyly). J Med Genet 3:104–113.

Weldon VV, Gupta SK, Klingesmith G, Clarke WL, Ducks SC, Haymond MW, Pagliara AS (1975): Evaluation of growth hormone release in children using arginine and L-dopa in combination. J Pediatr 87:540–546.

Yunis E, Varón H (1980): Cleidocranial dysostosis, severe micrognathia, bilateral absence of thumbs and first metatarsal bone, and distal aphalangia a new genetic syndrome. Am J Dis Child 134:649–653.

Edited by John M. Opitz and James F. Reynolds