

Clinical Report

Juberg–Hayward Syndrome: Report of a New Patient With Severe Phenotype and Novel Clinical Features

Peter Hedera¹ and Jeffrey W. Innis^{1,2*}

¹Department of Pediatrics, Division of Genetics, University of Michigan, Ann Arbor, Michigan

²Department of Human Genetics, University of Michigan, Ann Arbor, Michigan

We report a patient with severe mental retardation (MR), microcephaly, Dandy–Walker malformation, bilateral lip/palate clefts, hypertrophied sublingual frenulum, lobular tongue, absent thumbs, and other skeletal abnormalities, including Y-shaped metacarpals and urogenital abnormalities. High-resolution karyotype and subtelomeric fluorescence in situ hybridization were normal. We propose that his clinical picture is most consistent with Juberg–Hayward or orocraniodigital syndrome. Several clinical features present in our patient (unilateral distal displacement of elbow position, second-site radioulnar synostosis, bilateral Y-shaped metacarpal, lobular tongue, hypertrophic frenuli, Dandy–Walker malformation) have not previously been reported in this condition, thus expanding the phenotypic spectrum of this rare condition. The presence of these novel findings suggests possible overlap with other syndromes, such as orofacioidigital and Malpuech syndromes.

© 2003 Wiley-Liss, Inc.

KEY WORDS: orofacioidigital syndrome; malpuech syndrome; multiple congenital anomalies

INTRODUCTION

Juberg–Hayward syndrome (JHS), also known as orocraniodigital syndrome (OMIM #216100) is a rare condition that encompasses microcephaly, palatal/lip clefts, and thumb abnormalities [Juberg and Hayward, 1969]. Even though only a handful of patients have been reported, it is apparent that the severity of congenital anomalies varies considerably among affected individuals. This phenotypic variability was first evident in the original report that described five affected siblings from a sibship of six: two males had microcephaly, distally placed thumbs, radioulnar synostosis, and cleft lip and palate. Their two sisters had only minor toe abnormalities and one had forme fruste cleft lip; the third affected female had a transitional clinical picture with microcephaly, limb abnormalities but without oral clefting [Juberg and Hayward, 1969]. These differences may not be attributable to sex limitations because a female patient with severe skeletal changes has been described [Nevin et al., 1981].

Intelligence is normal in the majority of patients with JHS. Verloes et al. described three unrelated patients with the diagnosis of JHS and one of the individuals, a girl, had severe mental retardation (MR) [Verloes et al., 1992]. There is no correlation between the skeletal abnormalities and the occurrence of other features [Nevin et al., 1981; Kingston et al., 1982; Verloes et al., 1992; Kantaputra and Mongkolchaisup, 1999].

Here, we report a patient whose clinical picture is most consistent with JHS but who has several features that were not previously reported in JHS. The presence of these novel findings in our patient, which overlap with other syndromes, suggests that they may be etiologically related to JHS.

CLINICAL REPORT

The patient was a full-term product of an unremarkable pregnancy born to a 22-year-old G2, P1 woman. His birth weight was 2,480 g (25th centile), head circumference was 33.5 cm (25th centile), and birth length is unknown. He did not experience any perinatal difficulties. At birth, he had bilateral palate and lip cleft, absent thumbs, club foot on the right, bilateral hip dislocation,

Peter Hedera's present address is Department of Neurology, Vanderbilt University, 465 21st Avenue South, 6140 MRB III, Nashville, TN 37232-8552.

E-mail: peter.hedera@vanderbilt.edu

*Correspondence to: Jeffrey W. Innis, M.D., Ph.D., Department of Human Genetics, 4811 Med Sciences II, Box 0618, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-0618.

E-mail: innis@umich.edu

Received 14 October 2002; Accepted 5 March 2003

DOI 10.1002/ajmg.a.20263

multiple joint contractures, undescended testes, and third degree hypospadias, all of which have been surgically repaired. A loud parasternal murmur and two-dimensional echocardiogram demonstrated a small ventricular septal defect. Routine metaphase karyotype at birth was normal.

The patient experienced significant developmental delay and was able to walk without support only at age 5 years. He did not acquire any expressive speech but was able to understand simple commands and point to express his needs. He never achieved toilet training but was able to feed himself. There was no history of psychomotor regression. The patient had several simple febrile seizures at age 2 years. Eight years later, his parents observed several episodes of brief unresponsiveness. He was treated with valproic acid and has had no recurrence of seizures.

He was diagnosed with a non-progressive bilateral hearing loss estimated to be in the moderate range. At age 7 years, he was diagnosed with cholesteatoma in the right middle ear; subsequent surgery resulted in a total hearing loss on the right side. Follow-up echocardiograms demonstrated a spontaneous closure of the ventricular septal defect. The patient had signs of significant dextroscoliosis since he was able to walk and he never achieved a fully erect posture. Scoliosis was progressive and at age 14 years, he underwent successful placement of Harrington rods.

Both parents were healthy and their examination was normal. There was no history of consanguinity or pregnancy loss. The patient was the second of four children. He had one older brother and two sisters; his siblings were healthy with normal psychomotor development and their examinations were unremarkable.

Physical examination at age 14 years demonstrated a cachectic appearance with weight of 22.5 kg (<5th centile, 50th centile for a 7-year-old male) and estimated height 145 cm (<5th centile, 50th centile for a 12-year-old male); the height needed to be estimated secondary to severe scoliosis. Head circumference was 49 cm (<5th centile, 50th centile for a 2-year-old male). He had a slightly prominent metopic suture, prominent occiput, and bitemporal narrowing. Both ears were posteriorly angulated with an overfolded helix; no preauricular tags or pits were present. The interpupillary distance was 5.5 cm (>95 centile when corrected for microcephaly) and he had bilateral partial synechia of the lids due to chronic pterygion since age 12 years. Additional facial features included a prominent broad nasal root with parallel lateral edges and a bulbous tip, and a prominent chin. The tongue was lobular (Fig. 1).

The patient had marked skeletal abnormalities, including severe dextro-convex kyphoscoliosis, flexion contractures in both elbows with extension limited to 90° on the left and 140° on the right, bilaterally absent thumbs and marked camptodactyly of fingers 2–4 (Fig. 2). The total length of both arms was similar. The proportions between the two segments of the right arm were normal (upper arm 30 cm and forearm 23 cm); however, the left elbow was positioned more distally resulting in an upper arm length of 33 cm and a forearm length of 19 cm (<5th centile) and there was limited



Fig. 1. Photograph of the patient showing facial features, severe scoliosis, and contractures of both elbows.

extension at the elbow. Supination was markedly limited to 90° only on both sides. Examination of the lower extremities demonstrated contractures in both knees with extension limited to approximately 135°; he also had prominent genu valgum bilaterally. In the feet,



Fig. 2. Photograph of the patient attempting to fully extend both elbows demonstrating contracture of left elbow and distal position of the left elbow creating shortening of the left forearm.

the great toes were present, second toes were hypoplastic and there was mild cutaneous 2/3 syndactyly.

Neurologic examination was notable for lack of expressive language with partial preservation of perceptive language. He had congenital pendular nystagmus. No signs of pyramidal or extrapyramidal abnormalities were present. His gait was ataxic with occasional truncal titubation.

Radiologic examination was remarkable for bilateral radio-ulnar synostosis with a second site of radio-ulnar synostosis in the midportion of the right forearm. Both thumbs and first metacarpals were absent; second and third metacarpals were unremarkable. However, there was a common Y-shaped metacarpal, dividing into fourth and fifth metacarpals (Fig. 3). In the feet, the right, second metatarsal was slightly disproportionately long. Radiographs of the spine demonstrated a severe dextro-scoliosis without any vertebral segmental abnormalities; the ribs were unremarkable. Cranial axial computerized tomography of the brain demonstrated Dandy-Walker malformation. Temporal bone CT revealed poorly formed external auditory canals; the internal auditory canals were symmetrical, vestibules were prominent, cochleas were well formed, and the semicircular canals were normal. Renal ultrasound was unremarkable. Urine metabolic screen, quantitative plasma amino-acids and plasma 7-dehydrocholesterol were normal. A prometaphase karyotype, performed at the resolution of 750–800 bands was normal with a male 46,XY chromosomal constitution. Fluorescence in situ hybridization using subtelomeric probes (Boston University) was negative for any cryptic rearrangements or deletions.

Diepoxybutane-induced chromosomal breakage studies (A. Auerbach, Rockefeller University, NY) were normal.

DISCUSSION

We report a patient with absent thumbs, bilateral palatal/lip clefts, and microcephaly. These are cardinal



Fig. 3. Radiograph of both hands showing bilaterally absent thumbs and first metacarpals, bilateral common, postaxial, Y-shaped metacarpal, dividing into fourth and fifth metacarpals and severe camptodactyly of 2–4 fingers on the left hand.

features of JHS and we propose that this is the most likely diagnosis. Additional clinical findings supporting the diagnosis include the facial appearance with prominent glabella and wide nasal bridge, hypertelorism, limited elbow extension, radioulnar synostosis, and MR [Verloes et al., 1992].

Our patient had marked skeletal abnormalities, including absent thumbs, bilateral radioulnar synostosis and severe, progressive scoliosis. Comparison with other reported cases of JHS suggests that his skeletal abnormalities are severe. Previously, patients with JHS with absent thumbs, bilateral deformities of the radial head resulting in elbow contractures and proximal radioulnar synostosis have been reported [Kingston et al., 1982; Verloes et al., 1992]; however, unilateral distal displacement of the position of the elbow, resulting in the asymmetry between the arm and forearm lengths and without upper extremity total length discrepancy, is a new clinical finding. We also detected a second site of radio-ulnar synostosis in the midportion of the right forearm, i.e., the limb with relatively normal upper/lower segment proportions. Another unique finding that has not previously been observed in patients with JHS is the presence of a Y-shaped metacarpal, giving the origin to the fourth and fifth fingers. Typically, central Y-shaped metacarpals with insertional central polydactyly is a cardinal feature of orofaci-digital syndrome VI (Varadi-Papp syndrome, OMIM #277170) [Varadi et al., 1980]; however, our patient had postaxial Y-shaped metacarpal and missing thumbs, features not described in Varadi-Papp syndrome. Interestingly, orofaci-digital syndrome VI is also associated with oral abnormalities, including lip/palatal cleft, lobular tongue and hypertrophic frenuli, and Dandy-Walker malformation. Furthermore, similar features can be also seen in orofaci-digital syndrome II (Mohr syndrome, OMIM #252100) as one patient with Y-shaped fourth metacarpals with possible Mohr syndrome and a single female case of orofaci-digital syndrome II with Dandy-Walker malformation and MR have been reported [Haumont and Pelc, 1983; Hsieh and Hou, 1999].

In summary, these additional features, previously not observed in patients with JHS may further expand the phenotypic spectrum of this rare condition and suggest a considerable overlap with orofaci-digital syndromes.

Urogenital abnormalities in JHS are relatively rare, and the most common finding is horseshoe kidney [Verloes et al., 1992]. Association of orofacial clefting, urogenital abnormalities, including hypospadias, and MR was described in several offspring in a consanguineous Gypsy family [Malpuech et al., 1983]. The presence of complete penoscrotal hypospadias and severe MR in our patient suggests overlap with Malpuech syndrome and this is the second patient with overlapping features between JHS and Malpuech syndrome [Reardon et al., 2001]; however, the presence of severe skeletal anomalies, including bilateral absent thumbs suggests that the diagnosis of JHS may be more appropriate for our patient.

In summary, we present a case with the diagnosis of JHS who had severe skeletal abnormalities and severe

MR. Moreover, we describe several new findings, including Dandy–Walker abnormality, hypospadias, and oral abnormalities that were not previously reported in JHS syndrome. These new clinical features further expand the phenotype of JHS and also suggest possible overlap of this rare entity with Malpuech and orofacioidigital (especially Varadi–Papp type and few cases of Mohr type) syndromes. Alternatively, our patient could represent a newly recognized, separate condition. Elucidation of molecular causes of JHS, Malpuech and orofacioidigital syndromes will answer this question and whether these genes belong to a common pathway.

REFERENCES

- Haumont D, Pelc S. 1983. The Mohr syndrome: Are there two variants? *Clin Genet* 24:41–46.
- Hsieh YC, Hou JW. 1999. Oral-facial-digital syndrome with Y-shaped fourth metacarpals and endocardial cushion defect. *Am J Med Genet* 86:278–281.
- Juberg RC, Hayward JR. 1969. A new familial syndrome of oral, cranial, and digital anomalies. *J Pediatr* 74:755–762.
- Kantaputra PN, Mongkolchaisup S. 1999. Juberg–Hayward syndrome: A new case report and clinical delineation of the syndrome. *Clin Dysmorphol* 8:123–127.
- Kingston HM, Hughes IA, Harper PS. 1982. Orocranioidigital (Juberg–Hayward) syndrome with growth hormone deficiency. *Arch Dis Child* 57:790–792.
- Malpuech G, Demeocq F, Palcoux JB, Vanlieferinghen P. 1983. A previously undescribed autosomal recessive multiple congenital anomalies/mental retardation (MCA/MR) syndrome with growth failure, lip/palate cleft(s), and urogenital anomalies. *Am J Med Genet* 16:475–480.
- Nevin NC, Henry P, Thomas PTS. 1981. A case of theocranioidigital (Juberg–Hayward) syndrome. *J Med Genet* 18:478–480.
- Reardon W, Hall CM, Gorman W. 2001. An atypical case suggesting the possibility of overlap between Malpuech and Juberg–Hayward syndromes. *Clin Dysmorphol* 10:123–128.
- Varadi V, Szabo L, Papp Z. 1980. Syndrome of polydactyly, cleft lip/palate or lingual lump, and psychomotor retardation in endogamic gypsies. *J Med Genet* 17:119–122.
- Verloes A, Le Merrer M, Davin JC, Wittamer P, Abrassart C, Bricteux G, Briard ML. 1992. The orocranioidigital syndrome of Juberg and Hayward. *J Med Genet* 29:262–265.