Case Report

Co-Occurrence of Achondroplasia and Down Syndrome: Genotype/Phenotype Association

Lilia Maria de Azevedo Moreira,[1]* Marcos A. Matos,[2] Patricia P. Schiper,[3] Acácia F.L. Carvalho,[1] Ivalda C. Gomes,[4] José C. Rolemberg,[5] Renata L.L. Ferreira de Lima,[1] and Maria B.P. Toralles[6]

[1]Laboratory of Human Genetics and Mutagenesis, Biology Institute, Federal University of Bahia, Salvador, Bahia, Brazil
[2]Bahia School of Medicine and Public Health, Salvador, Bahia, Brazil
[3]Genetics Department, State Center for Prevention and Rehabilitation of Deficiencies, Salvador, Bahia, Brazil
[4]Center for Studies of Neurological Care and Health, Salvador, Bahia, Brazil
[5]Neurology Department, Medical College, Federal University of Bahia, Salvador, Bahia, Brazil
[6]Laboratory of Medical Genetics, Professor Edgard Santos Hospital, Federal University of Bahia, Salvador, Bahia, Brazil

Received 27 August 2009; Revised 9 December 2009; Accepted 6 January 2010

BACKGROUND: This report describes the sixth case of an unusual association: Down syndrome with achondroplasia. It also analyzes the effects of both of these disorders on patient phenotype. **METHODS:** A male infant was evaluated for Down syndrome. His appearance also suggested a diagnosis of achondroplasia. The child was evaluated by physical examination, radiography, cytogenetic study, and mutation analysis. **RESULTS:** Chromosome analysis showed a karyotype of 47,XY,+21 in all 30 cells analyzed. Radiographic examination showed typical findings of achondroplasia, such as disproportionately large skull, shortening of limb segments, and lumbar lordosis. FGFR3 screening showed a heterozygous G1138A mutation. **CONCLUSIONS:** The interaction of these two distinct genetic disorders in the same patient produces a phenotype typical of each syndrome with some overlapping signs. This case represents de novo origin of two disorders that both may be parental-age related. *Birth Defects Research (Part A) 88:228–231, 2010.* © 2010 Wiley-Liss, Inc.

Key words: Down syndrome; achondroplasia; advanced paternal age; advanced maternal age; disease interaction

INTRODUCTION

Down syndrome (MIM 190685) is a common cytogenetic disorder with an estimated prevalence of 1 per 600 to 800 births (Mutton et al., 1998). Similarly, achondroplasia (MIM 100800) is the best known and most common autosomal dominant form of disproportionate dwarfism, with a frequency of 0.5 to 1.5 per 10,000 births (Orioli et al., 1995). Previous research by Andersen and Hauge (1989) in the county of Fyn in Denmark, determined the prevalence of generalized bone dysplasia by studying all children born during a 14-year period. The figures, which they referred to as *point-prevalence at birth*, showed that achondroplasia was less common than generally thought (1.3 per 100,000), whereas osteogenesis imperfecta (21.8), multiple epiphyseal dysplasia tarda (9.0), achondrogenesis (6.4), osteopetrosis (5.1), and thanatophoric dysplasia (3.8) were found to be more frequent. To find both Down syndrome and achondroplasia simultaneously in an individual is extremely rare, with few previous reports in the literature. This report documents a new case and discusses the interaction of these different genetic factors in the clinical picture is discussed.

CASE REPORT

The patient (Fig. 1), a male infant, was born at 37 weeks' gestation by cesarean section. He was the second child born to a 35-year-old mother (gravida 3, para 2, abortus 1) and a 41-year-old father. The parents were healthy and not consanguineous, and they denied the ex-

*Correspondence to: Lilia Maria de Azevedo Moreira, Laboratory of Human Genetics and Mutagenesis, Biology Institute, Federal University of Bahia, Barão de Geremoabo, st s/n Ondina- Salvador, BA, Brazil 40170-115.
E-mail: lazevedo@ufba.br
Published online 10 March 2010 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/bdra.20653

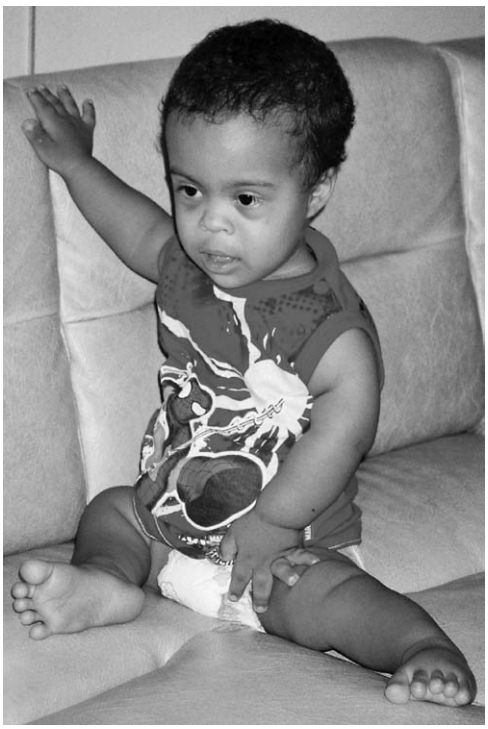

Figure 1. The patient at the age of 24 months.

istence of genetic abnormalities in their respective families. No alterations had been observed on antenatal ultrasonography. At birth, the infant was 50 cm long and weighed 3700 gm; the head circumference was not recorded. He was noted to have physical features typical of Down syndrome: hypotonia, upward-slanting palpebral fissures, depressed nasal bridge, a short neck with redundant skin folds of the nape, brachydactyly, left transverse palmar crease, bilateral fifth finger clinodactyly, and a plantar crease between the first and second toes. Echocardiography showed a patent foramen ovale. Ultrasonography of the upper abdomen disclosed mild gastroesophageal reflux. Culture of blood lymphocytes, with GTG banding showed the karyotype to be 47,XY,+21. The child also had a large head with frontal bossing, hyperextensibility of the joints, and rhizomelic shortening of the limbs. An additional diagnosis of achondroplasia was considered after the age of 16 months. Radiographic examination showed features typical of achondroplasia, such as marked macrocephaly with a shortened skull base, a small narrow sacrum, and lumbar lordosis (Fig. 2). Subsequent screening for a *FGFR3* gene mutation was performed by the PCR technique and showed a heterozygous *G1138A* mutation. At 24 months old, the child was small for his age (75 cm long; <3rd percentile). His head circumference was relatively large (48.5 cm; 50th to 85th percentile). He had a protuberant abdomen with a small umbilical hernia and diastasis recti. His chest was narrow with a mild compensatory thoracic gibbus. His limbs showed rhizomelia, and genu varum. He was healthy but susceptible to frequent respiratory infections. His thyroid function was normal (free thyroxine [T4L], 1.22 ng/dl; thyroid stimulating hormone [TSH], 2.63 μIU/ml). Although the child received physical therapy, including oral-motor and fine-motor skills, and early education since the first year of life, his acquisition of developmental motor milestones was delayed. He sat without support at 12 months old and stood at 15 months old.

Currently, at 28 months, he has begun to walk without support. He has universal hypotonia, predominantly in the hips and torso, with hypoactive deep tendon reflexes. He can roll and sit without support, and he has palmar prehension. There are apparent cognitive and communication impairments. He interacts with the environment with a playful and exploratory attitude. He responds to compression of the fingertips and touch of cold metal objects with a change of facial movements. He communicates by gestures, without any intelligible speech. He recognizes his name when called, recognizes songs, and understands and obeys simple orders. The vocalization of diphthong and shouts are delayed for age. To make requests, he uses nonverbal cues such as smiles, shouts with pleasant sounds, and head shaking. He shows sensitivity to light and auditory stimuli, without nystagmus or opsoclonus. He can differentiate people, objects, and photos. He shows interest in objects located in different points of space, and he maintains eye contact when spoken to.

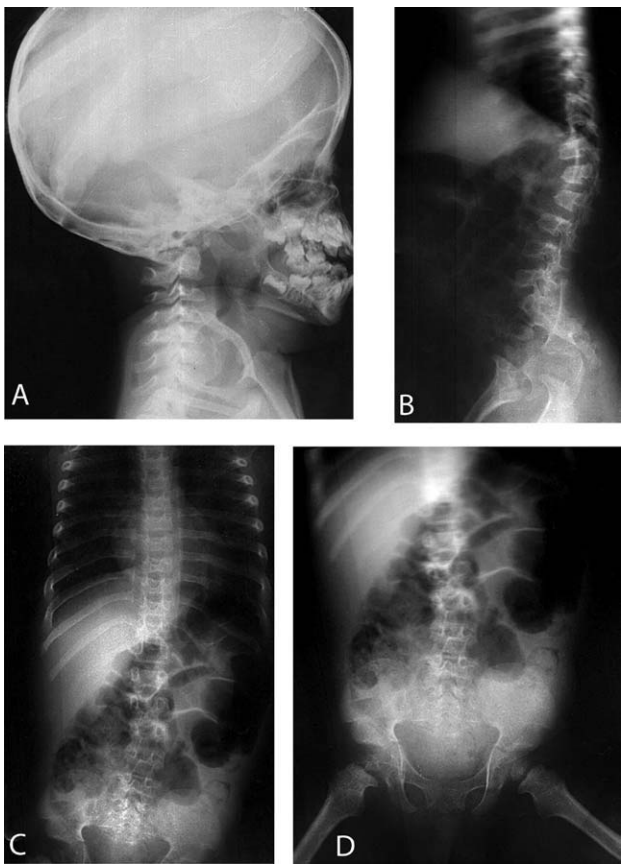

Figure 2. Radiographs of the 18-month old child showing characteristic achondroplasia features. (**A**) Large head with frontal bossing and midface hypoplasia. (**B**) Thoracolumbar kyphosis (T12-L2) and exaggerated lumbar lordosis with horizontal sacrum. (**C**) Spinal stenosis characterized by progressive narrowing of the interpedicular distance of the lumbar spine. (**D**) Short femoral neck, metaphyseal flaring, dysplastic ilium, narrow sacroiliac groove, and flat-roofed acetabula.

Table 1
Features Reported among Patients with Co-Occurring Down Syndrome and Achondroplasia

Features	Previously reported cases					Present case	Total
	Sommer and Eaton, 1970	Carakushansky et al, 1998	Sanchez and Guerra, 1999	Chen et al, 2000	Dabir et al, 2008		
Down Syndrome							
Developmental delay	+	+	+	+	+	+	6/6
Hypotonia	+	+	+	+	+	+	6/6
Flat face	+	+	+	+	+	+	6/6
Slanted eye fissures	+		+	+	+	+	5/5
Epicanthic eye-fold	+	+		+		+	4/4
Protruding tongue	+	+		−		+	3/4
Redundant neck skin			+	+		+	3/3
Heart disease	−	+		+	+	+	4/5
Transverse palmar crease	+		−	+		+	3/4
Clinodactyly of fifth digit	−		+			+	2/3
Gap between first and second toes	+		+	+		−	4/5
Plantar crease between the first and second toe						+	1/1
47,XX or XY,+21	+	+	+	+	−	+	5/6
46,XY,i(21)(q10)	−	−	−	−	+	−	1/6
Advanced maternal age (years)	17	43	36	33	41	35	4/6
Achondroplasia							
Severe small stature	+	+	+	+	+	+	6/6
Macrocephaly and craniofacial disproportion	+	+	+	+	+	+	6/6
Frontal bossing			+	+	+	+	4/4
Depressed nasal bridge	+	+	+	+	+	+	6/6
Hypoplasia half face		+	+	+		+	4/4
Narrow chest			+	+	+	+	4/4
Kyphosis thoracolumbar/ lordosis				+	+	+	3/3
Rhizomelia	+	+	+	+	+	+	6/6
Trident fingers			+	+	+	−	3/4
Pelvis: short sciatic notch	+		+	+		+	4/4
Mutation G1138A at FGFR3 gene				+	+	+	3/3
Advanced paternal age (years)	18	43	43	53	43	41	5/6
Survival of the patient	Live	Live	Dead at 4 month	Live	Dead at 5 months	Live	4/6

+, positive findings; −, negative findings; blank space indicates that this feature was not mentioned.

DISCUSSION

These conditions are relatively frequent by themselves, but co-occurrence of the two conditions in the same patient is rather rare. This case of Down syndrome with achondroplasia is the sixth to be reported since the first report by Sommer and Eaton in 1970. The clinical features observed in this and previously reported cases are summarized in Table 1. In all previous cases of this association, the diagnosis of trisomy 21 was confirmed by karyotyping. In these cases, the clinical and radiologic features were also characteristic of achondroplasia. The achondroplasia locus was mapped to chromosome 4p16.3 (Le Merrer et al., 1994; Velinov et al., 1994). The disorder is caused by mutation of the gene for fibroblast growth factor receptor 3 (*FGFR3*) in the transmembrane domain. Molecular techniques for *FGFR3* gene mutation screening were applied in only three patients (Chen et al., 2000; Dabir et al., 2008; and the present case). In all three, a single copy of the most common *G1138A* mutation was found: a G-to-A transition at nucleotide 1138, resulting in the substitution of glycine by arginine at position 380 (Gly380Arg) of the mature protein. The rarity of the combination of these disorders could be explained by factors such as increased prenatal mortality, failure to diagnose (Sanchez and Guerra, 1999), or by the low expected frequency of both conditions.

The presence of the two disorders in the same patient provides an opportunity to analyze the genotype-phenotype correlation and interaction in this unusual association. Although Down syndrome and achondroplasia have some characteristics in common, such as delayed motor milestones, a depressed nasal bridge, and brachydactyly, distinct signs of each condition are prominent in all patients. The achondroplastic features predominate in the skeletal structures, while other characteristics, such as facial morphology, are typical of Down syndrome. Speech delay, while not uncommon in Down syndrome, and articulation problems are possibly related to the midface hypoplasia found with achondroplasia. These problems are found in approximately 25% of achondroplasia cases (Hunter et al., 1998). Because of midface underdevelopment, the pharynx is small and the adenoids are large for the available space (Cohen et al., 1985). For this reason, or more likely owing to upper airway obstruction in achondroplasia, sleep dysfunctions including snoring and apnea may also be problems in infancy. In the families studied, the achondroplasia and Down syndrome each occurred as new mutations; none of the parents had a family history of genetic diseases. Advanced maternal age is a commonly recognized risk factor for trisomy 21. According to Wilkin et al. (1998) in sporadic cases of achondroplasia, de novo FGFR3 guanine 1138 mutations (over 97% of

cases) occur exclusively in the father's germ line. The mutations responsible for achondroplasia have been associated with advanced paternal age (Horton et al., 2007). The role of advanced paternal age in the incidence of achondroplasia and some other monogenic diseases, such as osteogenesis imperfecta and Apert, Crouzon, and Pfeiffer syndromes, depends on the hypothesis that spontaneous mutations accumulate because of continuous cell division during spermatogenesis (Astolfi et al., 2004). We considered these associations and note that the maternal and paternal ages were <35 years in only two cases (Sommer and Eaton, 1970; Chen et al., 2000). A multidisciplinary supervisory team to provide anticipatory care and management of his health and educational difficulties continues to monitor this child. We believe his prognosis is good, within the known cognitive limitations.

ACKNOWLEDGMENTS

The authors thank the family of the patient for their invaluable cooperation in the study.

REFERENCES

Andersen PE Jr, Hauge M. 1989. Congenital generalized bone dysplasias: a clinical, radiological, and epidemiological survey. J Med Genet 27:37–44.

Astolfi P, De Pasquale A, Zonta LA, et al. 2004. Late paternity and stillbirth risk. Hum Reprod 19:2497–2501.

Carakushansky G, Rosembaum S, Ribeiro MG, et al. 1998. Achondroplasia associated with Down syndrome. Am J Med Genet 77:168–169.

Chen H, Mu X, Sonoda T, et al. 2000. FGFR3 gene mutation (Gly 380 Arg) with Achondroplasia and i(21q) Down Syndrome: phenotype-genotype correlation. Southern Med J 93:622–624.

Cohen MM Jr, Walker GF, Phillips C, et al. 1985. A morphometric analysis of the craniofacial configuration in achondroplasia. J Craniofac Genet Dev Biol Suppl 1:139–165.

Dabir T, McCrossan BA, Sweeney L, et al. 2008. Down Syndrome, achondroplasia and tetralogy of Fallot. Neonatology 94:68–70.

Horton WA, Hall JG, Hecht JT. Achondroplasia. Lancet 2007; 370:162–172.

Hunter AG, Bankier A, Rogers JG, Sillence D, Scott CL Jr. 1998. Medical complications of achondroplasia: a multicentre patient review. J Med Genet 35:705–712.

Le Merrer M, Rousseau F, Legeai-Mallet L, et al. 1994. A gene for achondroplasia-hypochondroplasia maps to chromosome 4p. Nat Genet 6:318–321.

Mutton D, Ide RG, Alberman ED, et al. 1998. Changing trends in prenatal screening and diagnosis of Down's syndrome. BMJ 317:922–923.

Orioli IM, Castilla EE, Scarano G, et al. 1995. Effect of paternal age in achondroplasia, thanatophoric dysplasia, and osteogenesis imperfecta. Am J Med Genet 59:209–217.

Sanchez O, Guerra D. 1999. Acondroplasia y síndrome de Down en un mismo paciente: reporte de un caso. Invest Clin 40:143–154.

Sommer A, Eaton AP. 1970. Achondroplasia and Down's syndrome. J Med Genet 7:63–66.

Wilkin D, Szabo J, Cameron R, et al. 1998. Mutations in fibroblast growth-factor receptor 3 in sporadic cases of achondroplasia occur exclusively on the paternally derived chromosome. Am J Hum Genet 63:711–716.