CLINICAL REPORT

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Richieri-Costa and Pereira Syndrome: Severe Phenotype

Salmo Raskin,[1,2]* Marcela Souza,[3] Mariana C. Medeiros,[3] Mayra Manfron,[3] and Debora C. Chong e Silva[4]

[1]Clinical Geneticist, Hospital Pequeno Príncipe, Curitiba, Brazil

[2]Group for Advanced Molecular Investigation (NIMA), Graduate Program in Health Science (PPGCS), Health and Biosciences School (ESB), Pontifícia Universidade Católica do Paraná (PUCPR), Curitiba, Brazil

[3]Medical Student, Pontifícia Universidade Católica do Paraná, Curitiba, Brazil

[4]Pediatric Pneumologist, Hospital Pequeno Príncipe, Curitiba, Brazil

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Richieri-Costa and Pereira syndrome, described in 1992, comprises short stature, Robin sequence, cleft mandible, limb malformations, and short larynx, deformed or lack of epiglottis, and abnormal aryepiglottic folds. There are 32 reported cases, only one described outside Brazil. We describe a 4-month-old boy with the most severe phenotype yet reported. © 2013 Wiley Periodicals, Inc.

Key words: Richieri-Costa and Pereira syndrome; oral cleft; severe phenotype

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INTRODUCTION

The Richieri-Costa/Pereira syndrome (RCPS, OMIM 268305) was described in 1992 in five unrelated Brazilian females and was characterized by short stature, Robin sequence (micrognathia, glossoptosis, and cleft palate), cleft mandible and limb malformations. In 1993, the same authors described this syndrome in males [Richieri-Costa and Pereira, 1992, 1993]. History showed consanguinity and recurrence in sibs and a higher mortality rate in males, suggesting autosomal recessive inheritance of this condition. To the present, 32 Brazilian cases have been described [Richieri-Costa and Pereira, 1992, 1993; Tabith and Bento-Goncalves, 2003; Golbert et al., 2007; Graziadio et al., 2009; Favaro et al., 2011; Ogando et al., 2011; Souza et al., 2011; Tabith and Bento-Goncalves, 1996; Guion-Almeida and Richieri-Costa, 1998], and one non-Brazilian case [Walter-Nicolet et al., 1999]. The possibility of a common ancestry of these patients was raised [Favaro et al., 2011], and the possibility of allelic heterogeneity [Ferreira de Lima et al., 2003], Recently, a 16–20 nucleotides repeat at the 5′ UTR of the *EIF4AE* gene was identified as the mutation leading to RCPS [Favaro et al., 2012]. We report on a new Brazilian case involving a boy, with a very severe phenotype.

CLINICAL REPORT

This boy was born on January 17, 2012, in Matinhos, Paraná, Brazil. He was the first born of a first cousin consanguineous marriage; the mother was 17 years old and the father 26 years old, with no familial history of genetic disorders. Pre-natal care and ultrasound exams showed no fetal morphological alterations. Delivery was by Cesarean section at 38.5 weeks of gestation with no complications. The infant weighed 2,805 g, was 44 cm long, with a OFC of 31 cm and an Apgar score of five at 1 and 5 min, respectively. Malformations included: radial dysgenesis and finger anomalies (Fig. 1A,B), club feet, short limbs, toe anomalies (Fig. 1C), micrognathia (Fig. 1D), thoracic deformity with severe sterno–clavicular chondral bilateral dysfunction, fatty hyperplasia of the anterior and posterior surface of the neck, webbed neck,

Conflict of interest: none.

*Correspondence to:
Dr. Salmo Raskin, Laboratorio Genetika, GENETICS ALAMEDA AUGUSTO STELLFELD, 1516 Curitiba 80730-150, Brazil.
E-mail: genetika@genetika.com.br

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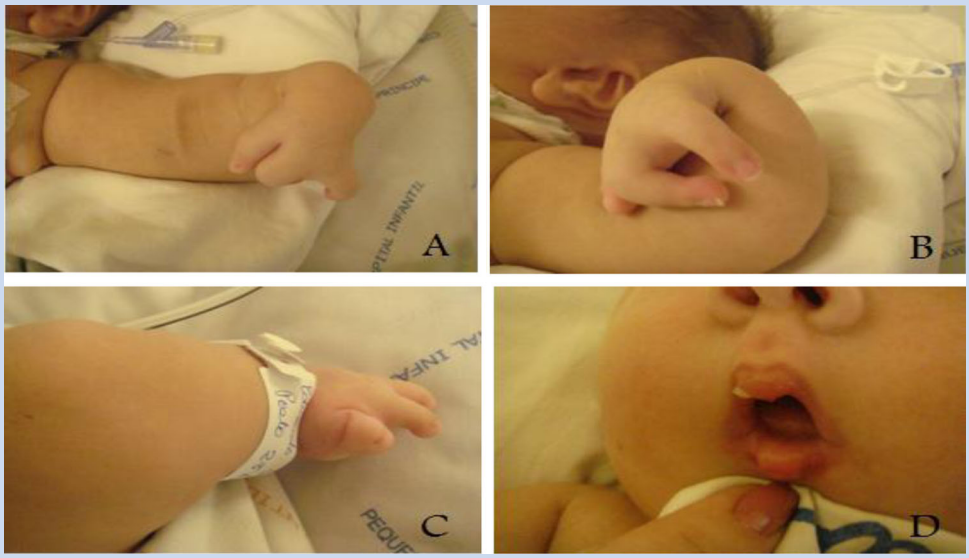

FIG. 1. Boy with RCPS. A,B: Upper limb deformities: radial dysgenesis, finger anomalies. C: Lower limb anomalies: congenital clubfeet, short limbs, and toe anomalies. D: Micrognathia.

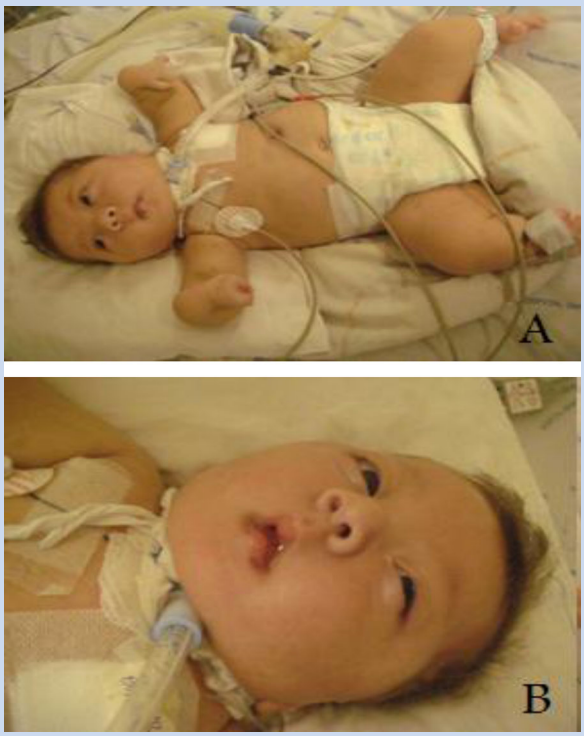

FIG. 2. Child's general state. A: Patient with tracheostomy and gastrostomy. B: Patient's face with micrognathia, microstomy, webbed neck, low-set ears and ear anomaly.

low-set ears, ear deformities, and cranio-facial pansynostosis evolving to craniosynostosis (Fig. 2A,B).

The patient remained hospitalized for 1 month due to ventilator need; he underwent tracheostomy and gastrostomy, and returned 2 weeks later to ventilator for 7 weeks due to respiratory failure and pneumonia.

On nasofibroscopy he had prolapse of base of tongue over the larynx and agenesis of the epiglottis; facial CT scan showed mandibular agenesis and deviated nasal septum. Limb radiographs (Fig. 3A,B) showed normal humerus, radial agenesis, hypoplastic ulna, normal femora, malformations of hands and fingers, normal pelvis, hyperplasia of the tibe, agenesis of fibulae, and toe deformities. There were no alterations in the urinary and gastrointestinal system. Neuropsychomotor growth and development were normal, compatible with the age and limitations of the patient. Tube feeding was necessary from the time of birth, due to anomalies of the airways. During the first hospitalization, the patient suffered a hypoxic cardiac arrest, with good response after cardiopulmonary resuscitation. He developed seizures, which were controlled pharmacologically. EEG showed moderately disorganized base activity for age in both cerebral hemispheres. Three-dimensional computed tomography scan showed agenesis of the anterior mandible arch and epiglottis (Figs. 4 and 5). Radiographs showed normal lungs, fractured right clavicle, and multiple rib fractures due to birth trauma. Hip ultrasound study showed slight subluxation of the right femoral head in relationship to the acetabulum during dynamic movements. These findings may be associated with immaturity due to the patients' age or due to hypotonia.

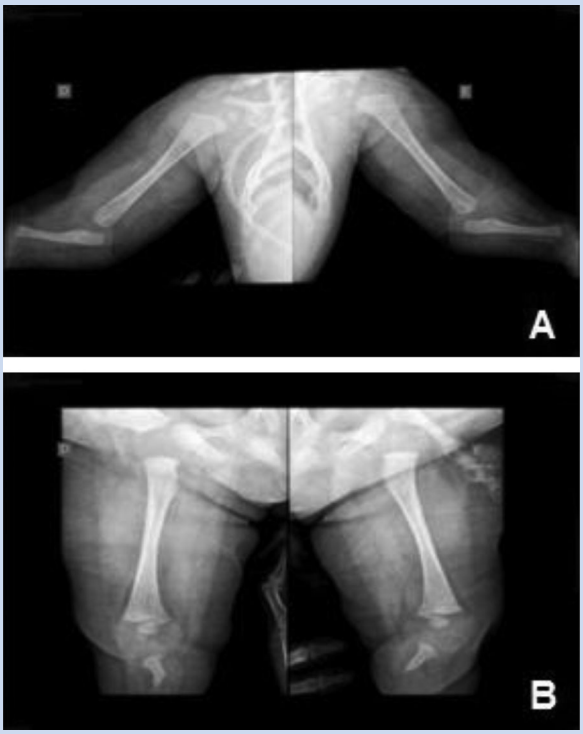

FIG. 3. Limb radiographs. A: Upper limbs, normal humerus. B: Lower limbs, normal femora, agenesis of fibulae, and normal pelvis.

On mastoid tomography opacification of the mastoid cells and of the tympanic membrane was identified. Cranial CT scan showed prominence of extra-axial space of the frontal convexity, ventricular system presenting normal morphological dimensions.

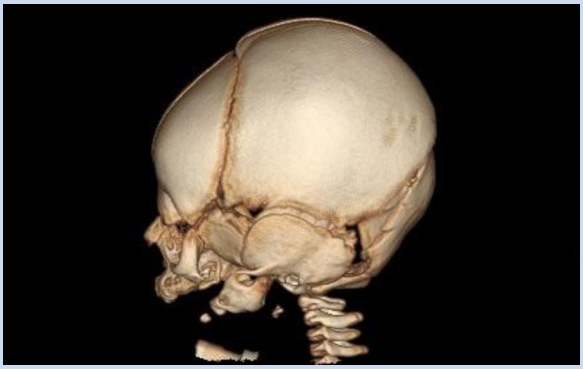

FIG. 4. Lateral craniofacial views at three-dimensional computed tomography scan showing metopic, sagital synostosis, agenesis of the anterior mandible arch and epiglottis.

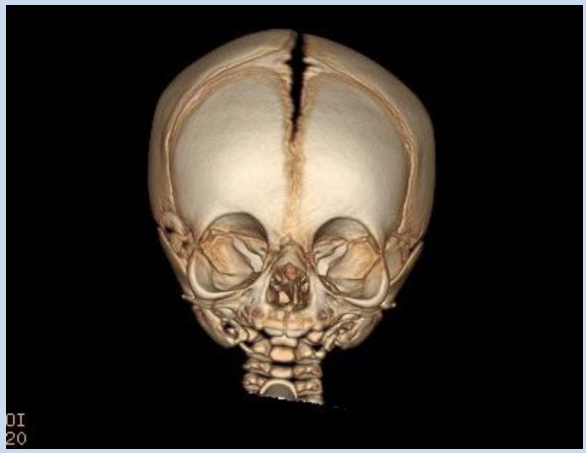

FIG. 5. Frontal craniofacial views at three-dimensional computed tomography scan showing agenesis of the anterior mandible arch and epiglottis.

The anatomic aspect of the basal cisterns, as well as fissures and sulci between the cortical gyri of the brain were normal. Alterations were observed in skull formation with overriding of lambdoid sutures. Currently the patient is 7 months old receiving infant formula (Nestle-NAN 2) by means of gastrostomy, supplemental oxygen (via tracheostomy), and was hospitalized two more times for respiratory difficulties.

DISCUSSION

After review of the 32 previously reported cases (Table I), we observed that there is a great variability in the expression from case to case, however, none reporting the same degree of severity as the present one. Although absence of Robin sequence and cleft mandible have been previously reported in several cases [Richieri-Costa and Pereira, 1992, 1993; Favaro et al., 2011], both malformations have often been described in this disorder, so their absence, particularly in a patient with a severe phenotype, raises issues of etiologic heterogeneity.

Although we understand that whenever consanguinity is involved atypical features can occur because of homozygosity of unrelated loci which can further confound clinical descriptors, this case shows that RCPS may present as a very severe phenotype, and given the severe deformities presented and their impact on quality of life, there is a need for further studies regarding this rare syndrome. The recent finding of a causative genetic alteration may generate information on the variability of expression and further elucidate the basis of severe phenotypes such as that reported in the present study.

TABLE I. Clinical and Radiological Characteristics of Known Patients

	This Report [2012]	Richieri-Costa and Pereira [1992]					Richieri-Costa and Pereira [1993]		Tabith and Bento-Goncalves [1996]		Richieri-Costa and Brandão-Almeida [1997]	Walter-Nicolet et al. [1999]	Tabith and Bento-Goncalves [2003]		Golbert et al. [2007]
Clinical findings															
Sex	M	F	F	F	F	F	M	M	F	F	F	M	F	F	F
Consanguinity	+	+	−	−	+	+	−	+	?	+	+	+	?	?	+
Age	4m	1y2m	1y1m	1y	3y	4y	8m	13y	11y	16y	10y	1d	9y	20y	3d
Neonatal respiratory distress	+	+	−	+	+	+	+	−	?	−	−	+	?	?	+
Short stature (postnatal)	?	+	+	+	+	+	+	+	+	+	+	?	?	?	?
Retromicrognatia	+	+	+	+	+	+	+	+	?	+	+	+	+	+	+
Microstomia	+	+	+	+	+	+	+	+	?	+	+	+	+	+	−
Cleft mandible	−	−	+	−	−	−	−	−	?	−	−	+	−	−	+
Cleft palate	−	−	−	+	+	+	−	−	?	+	+	−	−	+	−
Robin sequence	−	−	−	−	+	+	−	−	?	+	−	−	−	−	−
Laryngeal malformations	+	−	−	−	+	+	−	+	+	?	+	+	+	+	+
Hypoplastic radii	+	+	+	+	−	+	+	−	?	+	−	−	?	?-	−
Hypoplastic thumbs	+	+	+	+	+	+	+	−	?	+	+	+	?	?	+
Clinodactyly of 5th finger	+	+	+	−	−	+	−	−	?	+	+	+	?	?	+
Talipes	+	+	+	+	+	+	+	+	?	+	+	+	?	?	+
Others	A						B					C			D

	Graziadio et al. [2009]							Favaro et al. [2011]											Souza et al. [2011]	
Clinical findings																				
Sex	F	F	F	F	M	F	F	M	F	M	F	F	M	M	M	F	M	F	M	
Consanguinity	+	−	−	−	+	+	−	−	−	−	−	−	−	−	−	+	−	−	−	
Age	19y	17y5m	2y5m	2m5d	11y	9y9m	8y6m	5y11m	9m	4y3m	3y11m	2y9m	1y6m	9m	4m	48y	14d	6y	1y	
Neonatal respiratory distress	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	?	+	+	+	
Short stature (postnatal)	+	+	NE	+	+	+	+	+	+	+	+	+	+	+	NE	+	+	+	+	
Retromicrognatia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Microstomia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Cleft mandible	−	+	+	NE	+	+	−	+	NE	+	+	+	−	+	+	+		+	+	
Cleft palate	−	−	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	
Robin sequence	−	−	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	
Laryngeal malformations	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	+	+	
Hypoplastic radii	−	+	NE	NE	+	+	NE	+	+	+	+	+	+	+	NE	+	+	+	−	
Hypoplastic thumbs	+	+	+	NE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Clinodactyly of 5th finger	+	+	+	NE	+	−	+	−	−	+	+	+	+	+	+	+	−	+	+	
Talipes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	
Others	E																			

F, female; M, male; y, years; m, months; d, days; +, present; −, absent; NE, no evaluated; ?, unknown; A, thoracic deformity with high bilateral sternum chondral dysfunction, webbed neck, low set ears and ear deformities, cranial–facial pansynostosis, hip subluxation, malformation of the hands, fingers, and toes; B, lumbar lordosis and pectus excavatum; C, medial fissure, lower lip, campodactyly; D, hip subluxation aceptabular dysplasia and pseudoarthrosis of clavicle; E, pectus excavatum, scoliosis bilateral and fusion do 4th and 5th metacarpals.

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