Costello syndrome-associated orthopaedic manifestations focussed on kyphoscoliosis: a case series describing the natural course

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Costello syndrome (CS) is a rare genetic condition caused by a heterozygous mutation in the *HRAS* gene, with an estimated prevalence of 1: 300 000. Individuals with CS present with characteristic features including scoliosis, kyphosis, Chiari 1 malformation, and syringomyelia. The natural history of the spinal deformity associated with CS has been incompletely described. This case series describes the spinal deformity associated with CS and sets out a strategy for screening and treatment. The clinical records and spinal radiographs of nine consecutive CS patients encountered at a single centre were reviewed. Radiological assessments for the presence and progression of scoliosis were studied. Nine patients with confirmed CS were followed for a mean of 6.6 years. Five patients showed mild scoliosis. Two patients had lumbar kyphosis in addition to their scoliosis, and one showed scoliosis with proximal thoracic kyphosis. Three patients underwent investigation with MRI, one of which showed Chiari I malformation and a syrinx. One showed no change in the severity of their deformity over time. The remaining four patients showed a rate of increasing coronal deformity of 2.1° per year. There were no cases of rapid progression. All cases showed delayed skeletal maturity. The spinal deformity in CS appears to be slowly progressive. To identify those at risk of more rapid progression, brain and spine MRI should be carried out to exclude structural neurological abnormalities. Long follow-up is required for patients with spinal deformity in CS due to the delay in reaching skeletal maturity. Evidence level: 4. *J Pediatr Orthop B* 32: 357–362 Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Costello syndrome (CS) is a rare condition, first described in 1977 [1]. With an estimated prevalence of 1: 300 000 [1], the syndrome is characterized by short stature, severe feeding difficulties in infancy, coarse facial features (curly hair, relative macrocephaly, a depressed nasal bridge, and papillomata around the mouth and nares) (Fig. 1a and b), and an increased risk of malignancy (particularly rhabdomyosarcoma, neuroblastoma, and bladder carcinoma) [2], cardiac and neurological abnormalities, and intellectual disability [1]. It is caused by germline and somatic gain-of-function heterozygous mutations in the *HRAS* gene, which affects glycine residues in position 12 or 13 [3–5] of the RAS/mitogen-activated protein kinase (RAS/MAPK) pathway, collectively defined as RASopathy [3–6].

The orthopaedic manifestations of CS were reported in a 2003 study encompassing 16 participants, with each individual showing short stature and ligamentous laxity, and the majority showing a characteristic hand appearance (short, broad, and hyperextensible digits), reduced shoulder and elbow range of motion, tight Achilles tendons, and foot abnormalities [7]. Other findings included hip subluxation, pectus excavatum, and radial head subluxation [3–5,7–9].

Many patients with CS show spinal abnormalities such as scoliosis and kyphosis, the nature of which have been incompletely described because of the rarity of the syndrome [7]. It may be that these deformities are associated with neuraxial abnormalities, as hydrocephalus and syringomyelia are often seen in CS, with syringomyelia reported as a risk factor of progressive scoliosis [10,11]. However, the nature of this association is unknown and it may be the case that scoliosis is a consequence of the syndrome itself.

While appendicular skeletal abnormalities have been described in the literature, a comprehensive understanding of the spinal pathology remains absent. This report

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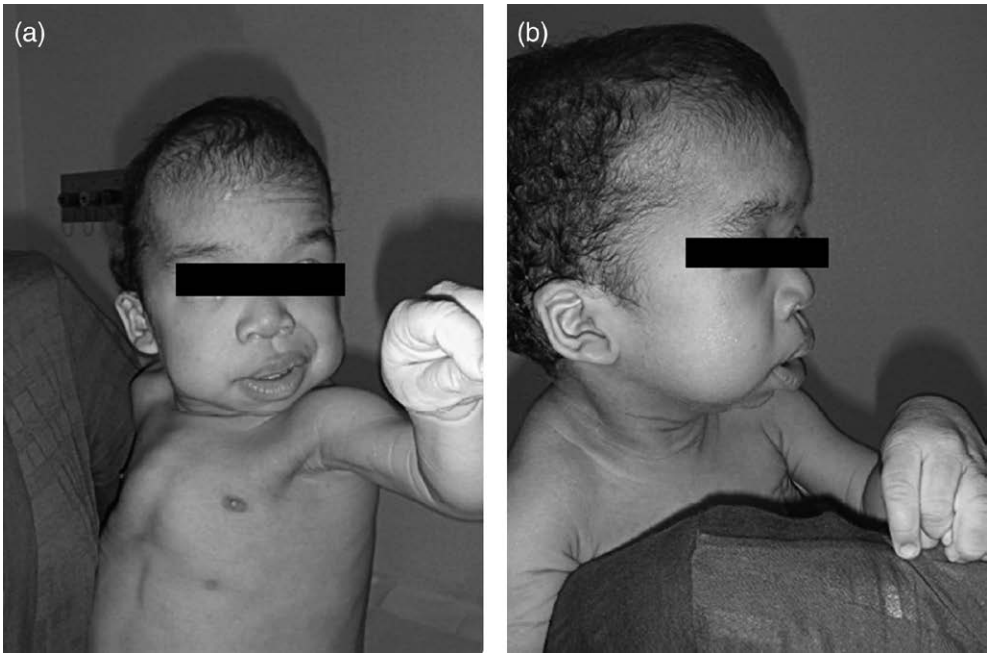
Fig. 1



(a and b) Facial features in Costello syndrome as curly hair, relative macrocephaly, a depressed nasal bridge and papillomata around the mouth and nares) (patient no. 7).

Table1 Patients demographics

	Number of patients
Total patients	9
Sex	
Male	5
Female	4
Average of age at first spinal evaluation	9.3 (range: 2.9–12.5)

defines the spinal abnormalities observed in CS in a consecutive case series and recommends a strategy for screening and treatment, both of which are essential for the precise management of these complex patients.

Materials and methods

Institutional research ethics board approval was obtained. A retrospective analysis of consecutive cases of CS encountered between 2010 and 2021. Patients were included only when CS had been genetically confirmed by observing *HRAS* mutation in a single institution. Patients were excluded if an alternative diagnosis was confirmed. Patient demographics and clinical data were identified from case records.

Long-cassette (36″) posteroanterior and lateral radiographs were used to assess the radiographic characteristics of the spine. Angular deformities were measured using the Cobb method, with deformity grouped into three categories using the most severe curve: mild scoliosis 10°–45°; moderate scoliosis 45°–60°, and severe scoliosis more than 60°. Thoracic kyphosis was measured from the superior endplate of T1 to the inferior endplate of T4 (T1-4) and the inferior endplate of T4 to the superior endplate of T12 (T4-12). Lumbar lordosis was similarly measured from the superior endplate of T12 to the endplate of S1. Skeletal maturity was assessed using Risser grade and assessment of the tri-radiate cartilage on the posteroanterior spine radiograph.

Results

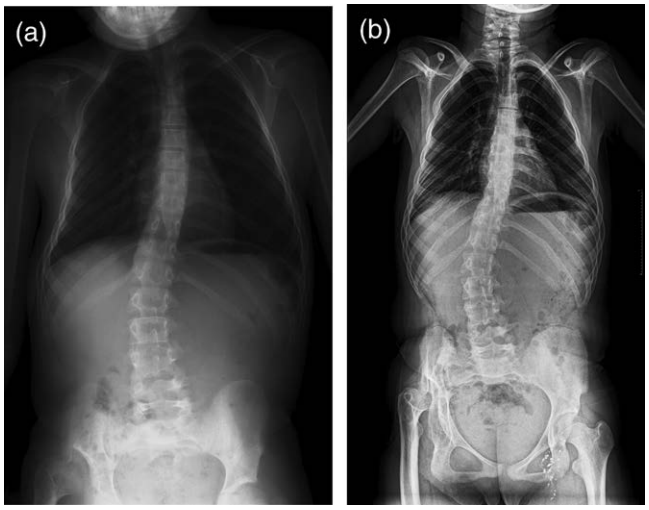
Nine patients were eligible for inclusion (five males and four females; Table 1), one of whom had the recurrent *HRAS* mutation c.38G>A (G13D), seven c.34G>A (G12S), and one c.34G>T (G12C). The mean age at first presentation was 8.7 years (range: 2.9–12.2 years). Six patients were able to independently stand for X-ray examination, two patients were necessarily supine, and one needed to sit (Table 2). Five patients showed mild scoliosis (one thoracic, one thoracolumbar, and three lumbar curves) (Fig. 2a and b). Two patients had a lumbar kyphosis in addition to their scoliosis and one showed scoliosis with proximal thoracic and lumbar kyphosis (Fig. 3a and b). Table 3 details the orthopaedic and spinal manifestations for each patient. Three patients underwent investigation with MRI due to an observed deficit in their abdominal reflex, one of which showed Chiari I malformation and a syrinx. This patient underwent foramen magnum decompression aged 9 years old prior to the diagnosis of

Table 2 **Overall spine measurements**

Patient No.	Age (year)	Sex	The position for X-Ray	*HARS* mutation	Cobb angle (°)	T1-4 (°)	T4-12 (°)	T12-S1 (°)	Risser grade	Tri-radiate cartilage	Sagittal balance	Scoliosis type
1	7.5	Female	Standing	c.38G>A (G13D)	4.6	ND	ND	ND	0	Unfused	-	Thoracic
	12.7				10.6	3.6	20.4	ND	0	Unfused		
	14.8				23.4	5.7	18.8	ND	0	Unfused		
	16.8				23.3	ND	ND	ND	0	Unfused		
2	10.8	Female	Standing	c.34G>A (G12S)	8.4	ND	ND	ND	0	Unfused	Upper thoracic kyphosis	Lumbar
	13.8				17.3	ND	ND	ND	0	Unfused		
	14.3				20	ND	ND	ND	0	Unfused		
	17.8				32	42.6	27.4	82.9	4	Fused		
3	8.1	Male	Supine	c.34G>A (G12S)	13.2	3.1	8.7	8	0	Unfused	Thoracic lordosis Lumbar kyphosis	Lumbar
	10.5				13.5	3.8	6.9	7.2	0	Unfused		
	12.6				15.9	4.9	4.2	7.2	0	Unfused		
	14.5				15.6	5.5	12.2	-8.9	0	Unfused		
	16.2				19.3	5.8	9.2	5.1	0	Unfused		
4	10.2	Male	Standing	c.34G>A (G12S)	2.2	ND	ND	ND	0	Unfused	-	Thoracolumbar
	14.4				8.6	ND	ND	ND	2	Fused		
	14.9				14.2	ND	ND	ND	2	Fused		
	15.7				14.9	7.6	34.9	43.8	4	Fused		
5	11.5	Female	Standing	c.34G>A (G12S)	9	ND	ND	ND	0	Unfused	-	Normal
6	11.7	Male	Standing	c.34G>A (G12S)	0	13.4	17.8	42.1	0	Unfused	-	Normal
	12.2				0	5.3	28.9	49.8	1	Unfused		
7	12.2	Male	Standing	c.34G>A (G12S)	6.4	ND	ND	ND	0	Unfused	Lumbar kyphosis	Lumbar
	14.4				9.7	7.1	29.3	-0.7	0	Unfused		
	16.5				10	4.4	24.8	-6.2	0	Unfused		
8	3.7		Supine	c.34G>A (G12S)	0	13.2	23.4	30.5	0	Unfused	-	Normal
9	2.9	Male	Sitting	c.34G>T (G12C)	0	ND	ND	ND		Unfused	-	Normal

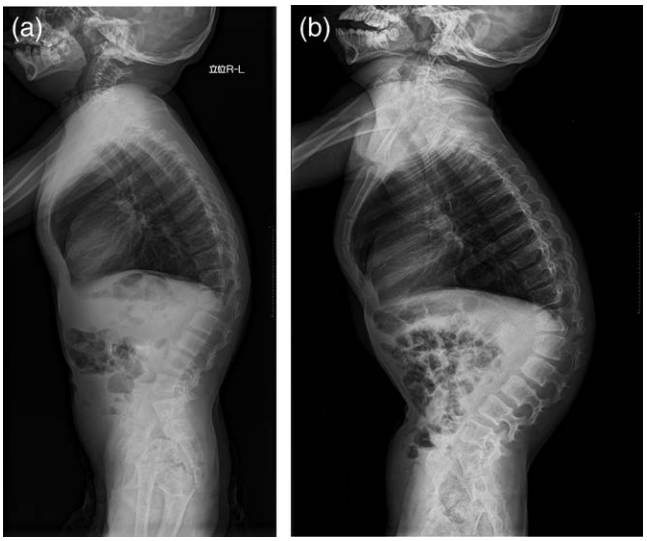
ND, no data.

Fig. 2



(a) A 13-year-old female with lumbar scoliosis (Cobb angle 17°), right hip dislocation, and Achilles tightness in standing position. (b) At 17 years, lumbar scoliosis (Cobb angle 31°) was mild progression for 4 years in standing position (patient no. 2).

Fig. 3



(a) A 14-year-old male with lumbar kyphosis (T12-S1 −0.7°) left hip dislocation and Achilles tightness in standing position. (patient no. 7). (b) At 16 years, lumbar kyphosis (T12-S1 −6.2°) was mild progression for 2 years.

scoliosis, with a later improvement in the appearance of the syrinx on MRI (Fig. 4a and b).

Each of the five individuals with scoliosis was followed for a mean of 6.6 years (range:4.3–9.3 years). Of these, one showed no change in the severity of their deformity over time and the remaining four patients showed a mean increase in coronal deformity of 2.1° per year (range: 0.8–3.4 years). All five of these cases showed a delay in reaching skeletal maturity. No patient required treatment with either an orthosis or surgery.

Discussion

This report describes the spinal deformity in CS and its progression over a minimum of 4 years. In this series, five of nine patients were diagnosed with mild spinal deformity, of which two showed accompanying sagittal plane malalignment. There were no cases of rapid progression of the spinal deformity observed.

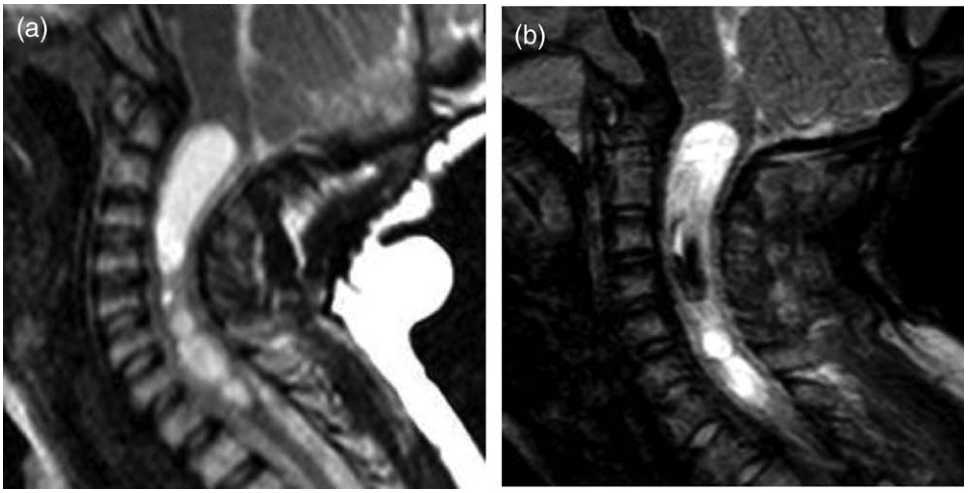
A previous report described the prevalence of scoliosis as 63% and kyphosis as 58% in patients with CS, similar to the values found in these data [3]. However, this report

Table 3 Details of the orthopaedic and spinal manifestations

Patient No.	Orhopaedic manifestations	Neurological deficit	MRI	Treatment
1	Achilles tightness	Abdominal reflex	Normal	
2	Right hip dislocation Achilles tightness	Abdominal reflex	Normal	
3	Right hip dislocation Achilles tightness	-	ND	
4	Achilles tightness	Abdominal reflex	Chiari type1	Foramen magnum decompression
5	Achilles tightness	-	ND	
6	Achilles tightness	-	ND	
7	Left hip dislocation Achilles tightness	-	ND	
8	Achilles tightness	-	ND	
9	Vertebra malformation in cervical	-	ND	

ND, no data.

Fig.4



(a) An 8-year-old male with Chiari I malformation and cervical syringomyelia visible on MRI. (b) Three years after undergoing foramen magnum decompression, the syringomyelia was partially improved (patient no. 4).

was unable to describe the length of follow-up or the rate of progression of a spinal deformity in patients with isolated CS. The data in this report show that the progression of spinal deformity in CS is slow.

In CS, postnatal cerebellar overgrowth can result in the development of Chiari 1 malformation with the associated hydrocephalus or syringomyelia possibly contributing to the more rapid progression of spinal deformity [5]. This may have been the situation with one case in this series (patient 4); however, this patient had undergone foramen magnum decompression before being diagnosed with scoliosis. Motosunehara *et al.* [10] reported a case of CS complicated by syringomyelia in which the coronal spinal deformity rapidly progressed from 32° to 101° within 22 months. However, this case report does not describe any treatment received for the neuraxial pathology. Similarly, Hou [12] reported a case of CS complicated by syringomyelia, which showed 56° progression of a coronal deformity over 3 months. This patient underwent surgical drainage for syringomyelia aged 8 years old after the rapid progression of the spine deformity had occurred.

As a consequence, these data lead us to recommend exclusion of structural neurological abnormalities when investigating these children in order to predict those at risk of rapid progression. Previously, MRI was recommended in CS to exclude the presence of syringomyelia [10]. However, patients with CS often require sedation for MRI in order to acquire precise images that can be accurately interpreted. Clinical clues to additional pathology include an absent or abnormal abdominal reflex, present in the majority of patients with a Chiari malformation type I associated syrinx, suggesting that the presence of this reflex may obviate the need for scanning [13].

The sagittal deformity in CS was assessed by Detweiler *et al.* [3]. This group reported lumbar kyphosis along with thoracic hypokyphosis and lordosis, effectively a reversal of the normal spinal curvature, which they concluded was characteristic of CS [3]. This conclusion is not supported

by these data, although the small cohort may be insufficient to refute the suggestion.

CS has been associated with impaired bone homeostasis, leading to diminished bone mineral density and reduced serum vitamin D concentration, which may impair bone maturation. This effect could be supplemental to the effects of RAS/MAPK pathway signalling dysregulation, which is closely associated with skeletal development, bone homeostasis, and remodelling [14–17]. An investigation that follows patients until skeletal maturity is required to completely characterize this phenomenon.

There are limitations in this study in addition to its retrospective design. It is important to emphasize that this study uses data from a small number of cases because of the rarity of the diagnosis. In addition, the follow-up period may be insufficient to clarify natural history of this complex syndrome. Furthermore, spinal evaluations are subject to measurement error and are impacted by a patient's ability to stand upright, which in some cases could be caused by hip dislocation or Achilles tendon tightness, both associated with CS.

In conclusion, this study sheds light on the spinal deformities common to CS. Although we should emphasize speculative nature of these conclusions, which are not based on the consecutive data, the spinal deformity appears to be static or slowly progressive when present. To prevent the risk of faster progression, an MRI investigation of both the brain and spine should be carried out to exclude structural neuraxial abnormalities when the abdominal reflex is absent. In addition, prolonged follow-up is required for patients with spinal deformity in CS due to delays in reaching skeletal maturity.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Costello JM. A new syndrome: mental subnormality and nasal papillomata. *Aust Paediatr J* 1977; **13**:114–118.
2 Gripp KW. Tumor predisposition in Costello syndrome. *Am J Med Genet C Semin Med Genet* 2005; **137C**:72–77.
3 Detweiler S, Thacker MM, Hopkins E, Conway L, Gripp KW. Orthopedic manifestations and implications for individuals with Costello syndrome. *Am J Med Genet A* 2013; **161A**:1940–1949.
4 Gripp KW, Lin AE. Costello syndrome: a Ras/mitogen activated protein kinase pathway syndrome (rasopathy) resulting from HRAS germline mutations. *Genet Med* 2012; **14**:285–292.
5 Aoki Y, Niihori T, Kawame H, Kurosawa K, Ohashi H, Tanaka Y, *et al*. Germline mutations in HRAS proto-oncogene cause Costello syndrome. *Nat Genet* 2005; **37**:1038–1040.
6 Kim YE, Baek ST. Neurodevelopmental aspects of RASopathies. *Mol Cells* 2019; **42**:441–447.
7 Yassir WK, Grottkau BE, Goldberg MJ. Costello syndrome: orthopaedic manifestations and functional health. *J Pediatr Orthop* 2003; **23**:94–98.
8 Gripp KW, Lin AE. Costello syndrome in: GeneReviews at GeneTests: Medical Genetics Information Resource [database online]. University of Washington, Seattle. 2006–2012. http://www.ncbi.nlm.nih.gov/books/NBK1507. [Accessed 15 March 2012]. Updated Jan 2012b.
9 Stevenson DA, Yang FC. The musculoskeletal phenotype of the RASopathies. *Am J Med Genet C Semin Med Genet* 2011; **157C**:90–103.
10 Motosuneya T, Asazuma T, Tsuji T, Watanabe H, Nakayama Y, Nemoto K. Severe scoliosis associated with Costello syndrome: a case report. *J Orthop Surg (Hong Kong)* 2006; **14**:346–349.
11 Sherk HH, Charney E, Pasquariello PD, Shut L, Gibbons PA. Hydrocephalus, cervical cord lesions, and spinal deformity. *Spine (Phila Pa 1976)* 1986; **11**:340–342.
12 Hou JW. Rapidly progressive scoliosis after successful treatment for osteopenia in Costello syndrome. *Am J Med Genet A* 2008; **146A**:393–396.
13 Nadel JL, Ziats C, Mossner JM, Starr JB, Smith BW, Kelly MP, *et al*. Superficial abdominal reflex in syringomyelia: associations with Chiari I malformation. *J Clin Neurosci* 2022; **98**:1–5.
14 Leoni C, Stevenson DA, Martini L, De Sanctis R, Mascolo G, Pantaleoni F, *et al*. Decreased bone mineral density in Costello syndrome. *Mol Genet Metab* 2014; **111**:41–45.
15 Stevenson DA, Schwarz EL, Carey JC, Viskochil DH, Hanson H, Bauer S, *et al*. Bone resorption in syndromes of the Ras/MAPK pathway. *Clin Genet* 2011; **80**:566–573.
16 Stevenson DA, Schwarz EL, Viskochil DH, Moyer-Mileur LJ, Murray M, Firth SD, *et al*. Evidence of increased bone resorption in neurofibromatosis type 1 using urinary pyridinium crosslink analysis. *Pediatr Res* 2008; **63**:697–701.
17 Yu X, Chen S, Potter OL, Murthy SM, Li J, Pulcini JM, *et al*. Neurofibromin and its inactivation of Ras are prerequisites for osteoblast functioning. *Bone* 2005; **36**:793–802.