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High Incidence of Progressive Postnatal Cerebellar Enlargement in Costello Syndrome: Brain Overgrowth Associated with *HRAS* Mutations as the Likely Cause of Structural Brain and Spinal Cord Abnormalities

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Abstract

Costello syndrome is a rasopathy caused by germline mutations in the proto-oncogene *HRAS*. Its presentation includes failure-to-thrive with macrocephaly, characteristic facial features, hypertrophic cardiomyopathy, papillomata, malignant tumors, and cognitive impairment. In a systematic review we found absolute or relative macrocephaly (100%), ventriculomegaly (50%), and other abnormalities on brain and spinal cord imaging studies in 27/28 individuals. Posterior fossa crowding with cerebellar tonsillar herniation (CBTH) was noted in 27/28 (96%), and in 10/17 (59%) with serial studies posterior fossa crowding progressed. Sequelae of posterior fossa crowding and CBTH included hydrocephalus requiring shunt or ventriculostomy (25%), Chiari 1 malformation (32%) and syrinx formation (25%).

Our data reveal macrocephaly with progressive frontal bossing and CBTH, documenting an ongoing process rather than a static congenital anomaly. Comparison of images obtained in young infants to subsequent studies demonstrated postnatal development of posterior fossa crowding. This process of evolving megalencephaly and cerebellar enlargement is in keeping with mouse model data, delineating abnormal genesis of neurons and glia, resulting in an increased number of astrocytes and enlarged brain volume. In Costello syndrome and macrocephaly-capillary malformation syndrome disproportionate brain growth is the main factor resulting in postnatal CBTH and Chiari 1 malformation.

Introduction

Costello syndrome encompasses severe failure-to-thrive, cardiac abnormalities including tachyarrhythmia and hypertrophic cardiomyopathy, a predisposition to papillomata and malignant tumors, and neurologic abnormalities including developmental delay, mental retardation, nystagmus and hypotonia [for review see Gripp and Lin, 2009; Quezada and

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Gripp, 2007]. It is caused by heterozygous germline mutations in the proto-oncogene *HRAS* [Aoki et al., 2005; Sol-Church and Gripp, 2009]. The *HRAS* protein is a key regulator of the mitogen activated protein kinase (MAPK) pathway, and Costello-associated missense mutations result in constitutive activation of the mutant protein and increased MAPK signaling. Mutations affecting other components of the MAPK pathway cause neurofibromatosis type 1 (NF1), Noonan syndrome, and cardio-facio-cutaneous (CFC) syndrome, amongst others. The shared mechanism of increased MAPK signaling represents the common denominator resulting in the overlapping phenotypes of these genetic syndromes collectively referred to as rasopathies. Relative macrocephaly and ventriculomegaly are common to these disorders, and Chiari 1 malformation has been reported in NF1 [Tubbs et al., 2004]; Noonan syndrome [Ball and Peiris; 1982; Holder-Espinasse and Winter, 2003], CFC syndrome [Yoon et al., 2007] and Costello syndrome [Gripp et al., 2002; Kerr et al., 2003; del Rue et al., 2003; Tubbs and Oakes 2003; White et al., 2005; Kerr et al., 2006; Zampino et al., 2006]. While cognitive impairment in Costello syndrome reflected by a mean brief IQ in the range of mild mental retardation has been studied in detail [Axelrad et al., 2004; Axelrad et al., 2007; Axelrad et al., 2009], structural brain abnormalities have not previously been systematically assessed. Here we review structural CNS anomalies in Costello syndrome, with particular attention to the posterior fossa and spinal cord.

Material and Methods

All available brain and spinal cord magnetic resonance imaging (MRI) studies were collected on patients enrolled in an ongoing study of Costello syndrome (A. I. duPont hospital IRB #2003-006 and #2005-051). Included in this analysis were all patients with a documented *HRAS* mutation for whom at least one imaging study of sufficient quality was available (Table I).

Results

Imaging studies on 28 individuals with Costello syndrome were systematically reviewed and correlated with available clinical information (Table II). All but one were abnormal with the most significant changes found in the posterior fossa.

Head size and brain growth

While complete measurements taken at birth were available in only 12 individuals, they indicate head size ranging from the 10th centile to >98th centile, and are only slightly greater than body length, which ranged from <3rd to 75th centile. Postnatal growth is poor, so that by 6-12 months length is consistently below the 3rd centile. In contrast, head circumference follows a normal curve or may cross centiles upward, resulting in head size that is disproportionately large compared to body size. The brain imaging features match this evolving disproportion, with bossed forehead and reduced extra-axial spaces apparent by 6-12 months. We defined relative macrocephaly as OFC 2 standard deviations (SD) or more above height centile for age, and found this in all subjects.

We interpret these changes as supporting abnormally rapid brain growth after birth. We found no apparent correlation between serial OFC measurements and the need for neurosurgical procedures (data not shown). In the absence of hydrocephalus or craniosynostosis, the disproportionately large head size suggests increased brain growth or megalencephaly as the driving force.

Ventriculomegaly

Enlarged lateral ventricles were noted on at least one imaging study in 14/28 (50%) individuals. Surgical intervention was required in 7/28 (25%) patients and consisted of shunt placement in six and third ventriculostomy in one. An intracranial bleed during treatment for a malignant tumor was the immediate cause for the shunt placement in one patient.

Cerebellar enlargement and its sequelae

Disproportion between cerebellar size and available space in the posterior fossa results in a crowded posterior fossa, which we define as a cerebellum enlarged relative to the posterior fossa, with cerebellar tissue filling the surrounding cisterns (extra-axial spaces), especially the cisterna magna in the lowest part of the posterior fossa. This is typically associated with herniation of the cerebellar tonsils and other inferior lobules down into the low posterior fossa, filling the cisterna magna and wrapping around the back of the low medulla and upper cervical cord. Posterior fossa crowding with cerebellar tonsillar herniation (CBTH) was noted on at least one imaging study in 27/28 (96%). In three individuals (ID# 29- LR08-371; ID# 188- LR09-031 and ID# 242- LR09-030) CBTH was not apparent on the first imaging studies obtained at age 1 week, 4 days and 6 months, respectively, but developed by the time of the second studies at 8, 12 and 15 months, respectively (Fig. 1). Progression of CBTH occurred in 10/17 (59%) individuals for whom a second study was available. In some patients, the herniation was associated with additional abnormalities including (1) compression of the medulla and high cervical cord with either subtle compression of the back of the brainstem resulting in a mildly concave shape or a more obvious focal compression, present in 11/28 (39%); (2) true Chiari 1 malformation with the cerebellar tonsils extending 5 mm or more below the level of the foramen magnum as seen in 9/28 (32%); or (3) syrinx or hydromyelia (dilatation of the central canal of the cord). A syrinx was noted in 7/28 (25%) individuals, even though imaging studies did not typically include the entire spinal cord.

Neurosurgical procedures

One or more neurosurgical procedures were performed in 13/28 (46%) patients, including shunt placement or ventriculostomy in seven individuals. Posterior fossa decompression was performed in 9/28 (32%) to relieve symptoms presumed due to compression of the low brainstem or upper cervical cord, or due to alterations in cerebrospinal fluid (CSF) flow secondary to CBTH. The symptoms typically associated with tonsillar herniation resemble the most common presentation of infants with Costello syndrome, including poor feeding, respiratory distress with mixed central and obstructive apnea, ocular palsy and constant arching. Older children sometimes report headaches, which may partly explain the severe irritability observed in younger children. Obstruction of CSF flow by the tonsillar herniation predisposes to development of a syrinx, which in turn increases the risk for progressive

scoliosis. In two patients, repeat posterior fossa decompressions were performed when they became symptomatic again with apparent headache and further enlargement of a syrinx (Fig. 2), resulting in increasing scoliosis and loss of hand strength. Tethered cord release was performed in 2/28 (7%).

Discussion

Structural central nervous system abnormalities, in particular delayed myelination, ventriculomegaly or hydrocephalus and tonsillar ectopia or Chiari 1 malformation, have previously been reported in patients with Costello syndrome [Gripp et al., 2002; Tubbs and Oakes, 2003; Delrue et al., 2003; White et al., 2005]. More recent cohort studies of patients with confirmed *HRAS* mutations include limited information on structural brain abnormalities. Our systematic review of brain and spinal cord images in individuals with a molecularly confirmed diagnosis of Costello syndrome provides new information on the incidence of these abnormalities, although some ascertainment bias is likely regarding which patients had imaging studies performed. In 27/28 patients, we found a consistent constellation of abnormalities including (1) accelerated postnatal brain growth in relation to body size, (2) prominent or bossed forehead, (3) ventriculomegaly, and (4) posterior fossa crowding with cerebellar tonsillar herniation. More severely affected individuals had known complications of CBTH including (5) hydrocephalus requiring shunt or ventriculostomy, (6) Chiari 1 malformation, and (7) syrinx formation. A few had tethered spinal cord, also associated with CBTH and Chiari 1 malformation [Milhorat et al., 2009]. These complications often required neurosurgical management with shunt placement or ventriculostomy, posterior fossa decompression, and tethered cord release. Serial studies revealed progression of the relative macrocephaly, frontal bossing and CBTH. This suggests accelerated postnatal (and possibly late prenatal) brain growth leading to relative megalencephaly, and supports an ongoing process rather than a static congenital anomaly. Most strikingly, comparison of imaging studies obtained in newborns to subsequent studies (Fig. 1) demonstrated postnatal development of posterior fossa crowding and CBTH. This apparent process of either postnatally arising or increasing posterior fossa crowding and CBTH can result in Chiari 1 malformation, with its sequelae of low brainstem-high cord compression, syrinx formation and associated neurologic symptoms. It is possible that the severe crowding in the posterior fossa decreases cerebrospinal fluid flow and absorption, resulting in the frequently associated ventricular enlargement and less common hydrocephalus. In several children in this series, we observed neurological sequela of brainstem-cord compression without Chiari 1 malformation or syrinx, as previously reported [Kyoshima et al., 2002]. The basis for tethered cord in several patients is less clear.

The majority of patients in our cohort (22/28; 78.5%) share the same mutation resulting in a heterozygous p.G12S amino acid change. Three individuals (3/28; 10.7%) had a p.G12A change, and three other mutations were seen in one person each. This distribution of mutations reflects the mutation spectrum and frequency reported in Costello syndrome individuals [Sol-Church and Gripp, 2009], and the preponderance of the most common mutation does not allow for more detailed genotype phenotype analysis.

Mouse model data

A review of the effect of Hras mutations on brain development in animal models supports our notion of postnatal cerebral and cerebellar overgrowth in individuals with Costello syndrome. Expression of constitutively activated p.G12V Hras in transgenic mouse neurons results in enlarged cortical brain volume, leading to caudal displacement of the cerebellum [Heumann et al., 2000]. The developmental mechanism resulting in these anatomic findings was elucidated by Paquin et al. [2009]. Expression of p.G12V and p.G12S in cortical progenitor cells in cell culture inhibited neurogenesis and promoted proliferation of cortical precursor cells and astrogenesis. In vivo expression in a mouse model also inhibited neurogenesis and promoted cell proliferation of cortical progenitor cells and additionally promoted premature gliogenesis. This premature formation of astrocytes at a time when gliogenesis has not yet normally begun led to a further increase of the number of astrocytes. In addition, some differentiated astrocytes were still proliferating in the mutant animals but not in controls. An increase in the total number of astrocytes was seen postnatally. Paquin et al. [2009] conclude that abnormal genesis of neurons and glia likely contributes to the cortical abnormalities and cognitive dysfunction in Costello syndrome. The process of evolving megalencephaly and cerebellar enlargement reported here is in keeping with this model.

Etiology of Chiari 1 malformation

The pathogenesis of CBTH and Chiari 1 malformation is only partly understood. Chiari 1 is a multifactorial condition generally attributed to a small posterior fossa, with reduced posterior fossa size due to either occipital bone hypoplasia (or dysplasia) or cranial settling associated with hypermobility of occipito-atlantal and atlanto-axial joints in many hereditary disorders of connective tissue [Stovner et al., 1993; Badie et al., 1995; Gripp et al., 1997; Nishikawa et al., 1997; Milhorat et al., 1999; Mesiwala et al., 2001; Milhorat et al., 2007; Noudel et al., 2009]. But these mechanisms are not sufficient to explain all cases of Chiari 1 malformation, as we now present data suggesting that in Costello syndrome, similar to macrocephaly-capillary malformation [Conway et al., 2007; Gripp et al., 2009], Chiari 1 malformation is associated with increased or relatively increased postnatal brain growth, leading to relatively enlarged cerebellum within a normal posterior fossa. It may be appropriate to reexamine the assumption that a Chiari 1 malformation is a congenital anomaly, and to view it as an abnormality resulting from an growth imbalance allowing for CBTH to occur and to progress over time, either pre- or postnatally. This hypothesis parallels that of Conway et al. [2007], who postulated that in macrocephaly-capillary malformation (M-CM) syndrome acquired CBTH results from a dynamic process of mechanical compromise in the posterior fossa, encompassing compromised CSF reabsorption. While individuals with M-CM and the closely related megalencephaly-polydactyly-polymicrogyria-hydrocephaly (MPPH) syndrome [Gripp et al., 2009] often have large head size at birth, their head circumference tends to increase dramatically after birth, and results in megalencephaly [Conway et al., 2007]. We hypothesize that similar to Costello syndrome, a process of abnormal neuro- and gliogenesis underlies similar findings in M-CM and MPPH, and speculate that these disorders could also be associated with dysregulation of the Ras-MAPK or related pathways.

The posterior fossa in other rasopathies

While the mouse model data support the notion of progressive brain overgrowth in Costello syndrome, it is less clear if this effect is *HRAS* mutation specific, or if it results from hyperactivation of the Ras/MAPK signaling pathway. Neurofibromatosis type 1 (NF1) is one of the more common rasopathies, and interestingly Chiari 1 malformation was found in 8.6% of 198 individuals who had brain imaging studies, suggesting a non-random association [Tubbs et al., 2004]. Chiari 1 malformation was also reported in several individuals with Noonan syndrome [Ball and Peiris, 1982; Holder-Espinasse and Winter, 2003], and in two patients with CFC syndrome [Yoon et al., 2007]. We saw Chiari 1 malformation in one individual with cardio-facio-cutaneous syndrome (Fig. 2). Relative macrocephaly is common to all these rasopathies, possibly suggesting a similar mechanism of abnormal neuro- and gliogenesis resulting in megalencephaly and at times in CBTH and Chiari 1. A review of serial imaging studies in individuals with these disorders may reveal progression rather than a static finding, similar to the course we describe in Costello syndrome.

Clinical impact

The need for neurosurgical procedures in 46% of individuals underscores a contribution to overall morbidity, and likely has a negative impact on the quality-of-life from the caregivers' perspective as shown by Hopkins et al. [2009; in press]. Two individuals required repeated posterior fossa decompressions, raising questions about the most appropriate surgical procedure, indication and timing. It is, however, clear at this time that in Costello syndrome CNS abnormalities are common, often progressive, and of significant medical impact. Thus we recommend baseline brain and spinal cord imaging in all patients with Costello syndrome at the time of diagnosis. Individuals with initial normal imaging in the first two years of life may develop significant CBTH thereafter. Thus, a repeat scan may be appropriate 1-2 years after the first scan. In older patients, repeat scans should be performed based on the initial brain imaging results and the clinical course, with particular attention to headaches, changes in gait or other neurologic problems. All individuals showing new onset of neurologic symptoms should be fully evaluated with brain and spinal cord MRI obtained as indicated, given that some newly symptomatic Chiari 1 malformations requiring posterior fossa decompression were identified in adults with Costello syndrome [White et al., 2005]. In light of the novel understanding that Chiari 1 malformation may represent a postnatal process rather than a static congenital anomaly, treatment approaches should be re-evaluated. Additional work may elucidate the best treatment option. Since the cerebellar enlargement shows significant postnatal progression, it may be amenable to pharmacotherapy geared towards amelioration of the hyperactivity of the Ras-MAPK pathway. Such therapeutic trials are likely to take place in the future, and their effect on cerebellar enlargement could become a measurable parameter for these studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Midline sagittal images in four normal controls (A-D) and six Costello patients (E-J), with ' and '' denoting subsequent studies. Progressive forehead bossing is seen in all six patients, but especially in E-E' and J-J''. Progressive posterior fossa crowding and cerebellar tonsillar (and often hemispheric) herniation is seen in all six patients. The white (or black in H-H') arrowheads point to cerebellar tissue in the lowest part of the posterior fossa, where it is not normally found. The herniated tissue may compress the low medulla and high cervical cord causing either subtle forward concavity (arrows in F'-F'', I'-I'' and J'-J'' for example) or frank compression (H-H', I'-I''). The dark round lesion in the cerebellar tonsil in one patient (upward arrow in F') represents post-surgical swelling. Severe tonsillar herniation led to Chiari 1 malformation and more severe medulla and cord compression with (top arrows in G'' and bottom arrow in J'') or without (H-H') Chiari 1 malformation. A few individuals developed syrinx of the upper cord, again with (G'', J'') or without (H-H') Chiari. The normal controls come from individuals DP97-043 (A), LR06-130 (B), LR07-264 (C) and LR09-129s1 (D). The Costello patients shown include ID# 29- LR08-371 (E-E'); ID# 43- LR09-058 (F-F''); ID# 255- LR08-284 (G-G''); ID# 13- LR08-409 (H-H'); ID# 1- LR08-408 (I-I'-I'') and ID# 188- LR09-031 (J-J'').

Figure 2a

Figure 2b

Figure 2.

Midline sagittal images in two patients with Costello syndrome (A-C), and one with cardio-facio-cutaneous syndrome (D) show severe complications of CBTH. Serial scans at 13 years (A) and 15 years (B) in patient 46 show CBTH (arrowheads) with compression of the ventral medulla and cord (arrows). The tonsils extend below the level of the foramen magnum on both scans, but this progresses from 3.7 mm at 13 years (A') to 5.7 mm at 15 years (B'); the latter exceeds 5 mm, meeting criteria for Chiari 1 malformation. The second scan in patient 13 at 5 years (C~) shows a cerebellar hemisphere completely filling the low posterior fossa (arrowheads), CBTH with minimal extension below the foramen magnum, ventral compression of the low medulla (top arrow), narrowing of the upper cervical cord over several cm starting just below the medulla, and a long syrinx (four lower arrows). The patient with CFC (D) has severe tonsillar herniation and Chiari 1 malformation (arrowhead) associated with a large syrinx (arrows). The subjects shown include ID#46- LR09-121 (A-A', B-B'), ID#13- LR08-409 (C~) and LR09-243 (D).

Table I
Patient Characteristics and Imaging Studies

Characteristic	Study
Number of individuals	N=28
HRAS mutation	
p.G12S	22
p.G12A	3
p.G13C	1
p.T58I	1
p.A146V	1
Sex	
Male	13
Female	15
Number of imaging studies	1 study: 7 >1 study: 21 (range 2–10 studies)
Mean age at first study	14–16 months (range 4 days–15 years)
Mean age at first repeat study	28 months (range 8 months–17 years)

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Table II

	20 ^a	22 ^a	29 ^a	32 ^a , b, i, j	42 ^b	43	46 ^k	47 ^b	48	170	181	184 ^l	187	188	198	213/	214	225	238 ^m	242	247	255	283	Total (%)
	G12S	G12S	G12S	G12A	G12S	G12S	G12S	G12S	G12S	G12S	G12S	T58I	G12S	G12S	G12S	A146V	G12S	G12S	G12S	G12A	G12S	G13C	G12A	
	+ R	+ R	+ R	+ R	+ R	+ R	+ R	+ R	+ R	+ R	+ R	+ A	+ R	+ R	+ R	+ R	+ A	+ R	+ R	+ R	+ R	+ R	+ R	28/28 (100%)
	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	27/28 (96%)
	-	+	+	-	-	+	-	+	-	-	-	-	+	-	-	-	-	+	-	+	+	+	+	14/28 (50%)
	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	27/28 (96%)
	N/A	+	+	N/A	-	+	N/A	-	N/A	+	-	N/A	-	+	N/A	N/A	-	-	+	+	-	+	N/A	10/17 (59%)
	+	-	-	-	-	+	+	-	-	-	-	-	-	+	-	-	-	+	+	-	-	+	+	11/28(39%)
	-	-	-	-	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-	-	+	+	+	9/28 (32%)
	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	+	-	-	+	+	7/28 (25%)
	sz	sz											Bleed											
	-	+	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	+	+	-	-	+	-	7/28(25%)
	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	+	-	-	+	+	9/28(32%)
	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	2/28(7%)

enlarged cerebellum relative to the space available in the posterior fossa, resulting in displacement of the cerebellar D refers to the Costello syndrome research study identifier. Sz: seizures. Macrocephaly was assessed on the most

>2.5 SD above mean for age. Relative macrocephaly was defined as OFC at least 2SD above height centile for age.

^mGripp et al. [2002].
^jGripp et al. [2008].
^kTubbs and Oakes [2003].
^jGripp et al. [2000].
^jWhite et al. [2005].
^qJohnson et al. [1998].

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