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Longitudinal Course of Cognitive, Adaptive and Behavioral Characteristics in Costello Syndrome

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Abstract

Costello syndrome is a rare rasopathy, caused by germline mutations in the oncogene *HRAS* resulting in increased signal transduction through the Ras/mitogen activated protein kinase pathway. In contrast to the more common rasopathies, such as neurofibromatosis type 1 and Noonan syndrome, limited information is available on standardized cognitive testing in this cohort. Past research indicated a mean average IQ in the mild mental retardation range, with strengths in Fluid Reasoning and weakness in expressive language, as well as static skills over time. Here we report on standardized IQ and adaptive functioning studies in 18 individuals with Costello syndrome, 9 male and 9 female, and longitudinal development for 11 who had previous testing. The overall IQ, ranging from severe mental retardation to the average range, with a mean in the mildly mentally retarded range, was again found to be stable, but an interesting pattern in the development of nonverbal fluid reasoning was identified. Participants showed an improvement in nonverbal fluid reasoning, followed by stable skills thereafter, suggesting a "late bloomer" effect in late childhood/early adolescence. Overall adaptive functioning fell into the range of Intellectual Disability for 70% of subjects, with Socialization as a relative strength and Daily Living Skills an area of relative difficulty. Interestingly, females were found to be higher functioning than males in all domains, including Communication, Daily Living Skills and Socialization. Caregivers reported significantly more behavioral concerns in males, including internalizing, externalizing and other maladaptive behaviors. In contrast, no gender differences were found in cognitive or visuomotor functioning.

Keywords

HRAS; p.G12A; p.G12S; p.G13C; p.T58I; longitudinal assessment; cognitive functioning; MAP kinase pathway

INTRODUCTION

Costello syndrome is due to heterozygous germline mutations in the *HRAS* gene. These missense mutations exert a gain-of-function on the abnormal protein product and result in

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increased signaling through the Ras-mitogen activated protein kinase (MAPK) pathway. Other syndromes resulting from mutations affecting the Ras-MAPK pathway include Noonan, Leopard, Cardio-Facio-Cutaneous syndrome, neurofibromatosis type 1 and the phenotype associated with *KRAS* mutations. The identification of a disease causing mutation in a patient confirms a clinical syndrome diagnosis, and may allow for a more accurate understanding and anticipation of associated medical and cognitive problems. Under the best of circumstances, this improved knowledge results in more accurate counseling, more effective medical care, improved outcome and better quality of life.

A recent study of cognitive profiles of patients with Ras-MAPK disorders reported test results of 44 patients with mutations in 7 different genes [Cesarini et al., 2009] and showed a relatively narrow range of global IQ scores for patients with Costello syndrome. Past research in Costello syndrome has indicated various intellectual strengths (Fluid Reasoning) [Axelrad et al., 2004] and weaknesses (expressive language) [Axelrad et al., 2007] as well as static skills over time with the exception of some possible gain in adaptive behavior, although this was possibly due to measurement error [Axelrad et al., 2007]. Due to the rarity of Costello syndrome, limited studies within age or gender cohorts have been performed.

Studies on larger cohorts of patients with mutations in each of the respective genes are necessary to achieve statistical relevance in comparing similarities and differences across Ras-MAPK disorders, as well as informing the literature regarding the longitudinal course of these disorders. Here we aim to provide such data on patients with Costello syndrome. The longitudinal nature of our study, with three consecutive evaluations over a six year period affords further insight into stability, decline, or development in the patient population, as well as the ability to look more specifically at age cohort and gender effects.

MATERIAL AND METHODS

Participants

Patients and families were contacted and evaluated through the 5th International Costello Syndrome Conference (2007). Only families speaking English as their primary language were included. Informed consent was obtained based on protocols approved by the institutional review boards at Texas Children's Hospital (H-17456) and the A. I. duPont Hospital for Children (#2003-006, #2005-051).

The 18 participants ranged in age from 4 years 0 months to 24 years 5 months, with a mean of 13 years 1 month and an SD of 81 months. There were 9 females and 9 males. All school aged participants were being formally educated within a school system. The older individuals participated in part-time paid or volunteer work. The Costello syndrome diagnosis was confirmed by identification of an *HRAS* mutation in all study subjects (Table 1).

Eleven of the 18 participants (61%) had been seen for prior cognitive testing at the 3rd International Costello Syndrome Conference [for details, see Axelrad et al., 2004], and 8 (44%) had been seen at both the 3rd and the 4th International Costello Syndrome Conference [for details, see Axelrad et al., 2007]. Seven subjects (39%) were seen for the first time, one of these was included in a previous publication [Gripp et al., 2008]. Five adults are also included in Hopkins et al. [2009]. Comparison of the results obtained at the different times, defined at T1 for evaluation in 2003, T2 in 2005, and T3 in 2007, allowed us to infer interim development.

Methods and Materials

Genomic DNA was extracted from buccal cells or peripheral white blood cells and tested for *HRAS* mutations as previously described [Gripp et al., 2006].

In order to assess cognition and memory, the Brief IQ and Associative Memory subtests from the Leiter International Performance Scale – Revised were administered [Roid and Miller, 1997]. The Leiter International Performance Scale – Revised is a standardized, reliable, and valid measure of nonverbal intellectual ability. Reported reliabilities of the Brief IQ range by age from .88 to .90, and reliabilities of the Associative Memory Index range by age from .79 to .81. Test-retest correlations for the IQ screener have been found to be .88 and above. Content validity, criterion-related validity, and construct validity have all been well researched with this test and consistent evidence of validity has been documented. Four subtests from the Leiter-R were used to compute the Brief IQ score. Two of the four subtests assess visual perceptual skills (Figure Ground, Form Completion), and two assess fluid reasoning skills (Repeated Patterns, Sequential Order). The Associative Memory Index is comprised of two subtests (Associated Pairs, Delayed Pairs). Raw scores for these subtests were added and converted to a standard score with a mean of 100 and SD of 15. A Fluid Reasoning score was calculated separately using the appropriate subtests.

Verbal intellectual functioning was assessed with verbal subtests of the Stanford Binet Intelligence Scales-5th Edition (SB5) [Roid, 2003a]. The SB5 is a standardized scale commonly used to assess intellectual functioning in individuals with cognitive and developmental disabilities, as it was designed to provide a wide range of assessment at the lower and higher ranges of the scale [Roid, 2003b]. The Verbal Domain Index Score (VIQ) has shown excellent reliability (with coefficients ranging from .94 to .97), test-retest stability (.93 to .95), and content validity, criterion-related validity, and construct validity [see Roid, 2003b for details]. The VIQ is composed of 5 subtests assessing discrete factors of intelligence (Fluid Reasoning, Knowledge, Quantitative Reasoning, Visual-Spatial Processing, Working Memory).

The Peabody Picture Vocabulary Test 4th Edition (PPVT-IV) [Dunn and Dunn, 2007] was used to assess one-word receptive vocabulary. This measure is standardized with evidence of good reliability and validity. The test consists of 228 test items grouped into 19 sets of 12 items. Each item consists of four full color drawings arranged on a page, and the test taker is asked to point to the picture that best represents the meaning of the stimulus word spoken by the examiner. Raw scores were converted to standard scores with a mean of 100 and SD of 15.

The Beery Developmental Test of Visual-Motor Integration (VMI) [Beery and Beery, 2004] is a standardized index of the ability to integrate visual-perceptual information with motor abilities, and is especially sensitive to difficulties at earlier ages. Norms are available for children age 2 years and up. The VMI has good overall internal reliability (Cronbach's $\alpha = .82$) and test-retest reliability ($r = .89$) across age groups. An optional subtest (VMI Visual Perception) provides additional information regarding visual-perceptual abilities without a motor component.

The Vineland-II Adaptive Behavior Scales Survey Interview Form [Sparrow et al., 2005] is a semistructured interview completed with the patient's caregiver/guardian. Items on the scale assess the ability to perform daily activities required for personal and social competence. Standard scores for Communication, Daily Living Skills, Socialization, and Motor Skills are attained. The Communication domain evaluates receptive, expressive, and written language skills. The Daily Living Skills domain assesses personal daily living skills, domestic daily living skills, and community skills. The Socialization domain assesses

interpersonal relations, play, and coping skills. The Motor Skills area assesses both fine and gross motor skills. For children under age 6 years, standard scores are attained for all areas. For older children, standard scores are attained for all areas except Motor Skills. An Adaptive Behavior Composite score taking all applicable domains into account was attained for all participants. Standard scores have a mean of 100 and SD of 15.

The Vineland-II Adaptive Behavior Scales Rating Form [Sparrow et al., 2005] was also used to determine behavioral profile. The Maladaptive Behavior Index includes scales indicating internalizing and externalizing difficulties. V-scores are obtained for these scales, which are then translated into descriptive categories (average, elevated, clinically significant). V-scores have a mean of 15 and SD of 3.

Procedure

The protocol was IRB approved by two institutions, and informed consent was obtained. Assent was obtained when possible, and participants were told they did not have to complete any of the measures. A psychological associate individually administered the subtests from the Leiter International Performance Scale-Revised, the PPVT-III and the EVT to each child. A clinical psychologist interviewed each caregiver/guardian using the the Vineland-II Adaptive Behavior Scales Survey Interview Form. Means, SDs, and ranges were calculated for all scores obtained using standard techniques.

RESULTS

Nonverbal cognitive abilities

Nonverbal intellectual abilities¹ for all 18 patients were assessed using the Leiter International Performance Scale-Revised – Brief IQ score. Consistent with prior findings, 78% of participants fell within the range of Intellectual Disability. Eleven percent (2 subjects) fell in the borderline range, 6% (1 subject) in the low-average range, and 6% (1 subject) in the average range (Fig. 1).

Nonverbal fluid reasoning (Leiter-R Fluid Reasoning Index; $n = 18$) ranged from the moderate range of Intellectual Disability to the average range (Mean = 65, SD = 17, range = 48 to 100). Consistent with prior findings, nonverbal fluid reasoning was found to be a strength relative to overall nonverbal IQ by about $\frac{1}{2}$ a standard deviation on average, though this effect was not statistically significant due to high within-group variance (Fig. 1).

Nonverbal memory (Leiter-R Associative Memory Scale; $n = 14$) was consistent with nonverbal intellectual functioning, with 43% of subjects falling in the mildly delayed range, 36% in the borderline range, and 21% in the low-average range (Fig. 1).

Verbal cognitive abilities

Verbal intellectual abilities (SB5; $n = 18$) were within the range of Intellectual Disability for 83% of participants, with 44% falling in the moderate range, and 39% in the mild range (Mean = 57, SD = 13, range = 43 to 90). Two subjects (11%) fell in the borderline range, and 1 (6%) in the average range. In contrast to the nonverbal test results, fluid reasoning in the verbal realm was not found to be a strength relative to overall verbal IQ ($F = 1.63$, $p = .2$) (Fig. 1).

¹Widely accepted standard score ranges for cognitive functioning are as follows (from APA, 1994): Profound Intellectual Disability: IQ level below 25; Severe Intellectual Disability: IQ 26–40; Moderate Intellectual Disability: IQ 41–55; Mild Intellectual Disability: IQ 56–69; Borderline: IQ 70–79, Low Average: IQ 80–89; and Average IQ 90–109.

Receptive vocabulary skills, as measured by the PPVT-IV ($n = 18$), were better developed than overall verbal cognitive skills. Fifty-five percent fell in the range of Intellectual Disability, with a third (33%) in the borderline range, and 2 subjects (11%) falling in the low average range (Mean = 63, SD = 15, range = 33 to 88).

Visuomotor skills

Visuomotor integration skills (VMI; $n = 18$) were in the range of Intellectual Disability for a majority of subjects (83%), with the remaining 17% falling in the borderline range. Non-motor visuoperceptual skills (VMI Visual Perception) showed a similar pattern, with 50% falling in the moderate range, 22% falling in the mild range, 11% falling in the borderline range, and 1 subject falling in the low average range.

Adaptive behavior

The Vineland-II Adaptive Behavior Scales (VABS-II) Survey Interview Form was completed for 17 subjects. Overall adaptive functioning was judged to fall in the range of Intellectual Disability for 70% of subjects, with 24% in the borderline range, and one subject (6%) in the low average range. Socialization skills were indicated as a relative strength (Mean = 75, SD = 12), and Daily Living Skills were an area of relative difficulty (Mean = 65, SD = 9), and the difference between these two scales was significant ($F = 7.466$, $p = .01$). Communication skills fell between these two ranges (Mean = 68, SD = 9).

The VABS-II Motor Scale was completed for the five children under age 7 years. Motor skills were rated as falling in the mild range of disability for all 5 subjects (Mean = 59, SD = 2).

The VABS-II behavioral profile was completed for 16 subjects. Twenty-five percent had internalizing scores in the Average range, 50% had Elevated internalizing scores, and 25% had Clinically Significant internalizing problems. Thirty-eight percent had externalizing scores in the Average range, whereas 56% had Elevated externalizing scores and one subject (6%) had a Clinically Significant externalizing score.

Difference by mutation

Because the disease causing mutations of two patients differ from the other patients' change (one male p.G13C, one male p.T58I), we reviewed their test results individually and compared them to the mean for the study group. On the Leiter-R measure, both patients scored more than 1 SD above the mean on the Fluid Reasoning scale. The patient with the p.G13C mutation also scored more than 1 SD above the mean on the Leiter-R Memory Screen and the PPVT-IV, and more than 3 SD above the mean on the SBV (scores ranging from the Low Average to Average range on these scales). The patient with the p.T58I scored more than 2 SD below the mean in the VABS-II Daily Living Skills, and more than 1.5 SD below the mean in VABS-II Socialization.

Age-cohort effects

To examine developmental trends, subjects were divided into three age groups: Child (age 10 years and under; $n = 6$), Adolescent (age 11 to 17; $n = 7$), and Adult (age 18 and up; $n = 5$) (see Table I). Overall, the Child group showed significantly better nonverbal cognitive functioning, with Leiter-R Brief IQ scores in the borderline range ($M = 72$) relative to the Adolescents who were in the mild range of disability ($M = 55$) and the Adults who were in the moderate range of disability ($M = 41$) ($F = 9.84$, $p < .002$). This trend appears largely driven by differences in nonverbal fluid reasoning, with the Child group falling in the low average range ($M = 81$), the Adolescent group in the mild range of disability ($M = 64$), and the Adult group falling in the moderate range ($M = 49$) ($F = 9.54$, $p = .002$). Relative

performance on the VMI also declined across age groups, with the Child and Adolescent groups falling in the mild range of disability and the Adult group falling in the moderate range ($F = 5.256$, $p = .02$). Interestingly, on the PPVT-IV, the opposite trend was observed, with the Adult group showing better relative verbal skills compared to the Child group, though this difference was only marginally significant ($F = 3.7$, $p = .09$). There were no age cohort effects in caregiver-reported adaptive functioning, though there was a non-significant trend toward greater maladaptive behaviors in the Child group ($F = 3.00$, $p = .08$) (Fig. 2).

Gender

A multivariate analysis of variance was performed to examine whether there was a difference in behavioral profile by gender. Significant differences emerged in caregiver-rated adaptive functioning. Specifically, females ($n = 9$) were found to be higher functioning than males ($n = 8$, one parent of a male did not participate in interview) in all domains, including Communication (Female $M = 73$, Male $M = 63$; $F = 11.509$, $p = .006$), Daily Living Skills (Female $M = 67$, Male $M = 62$; $F = 5.093$, $p = .045$), and Socialization (Female $M = 77$, Male $M = 70$; $F = 10.367$, $p = .008$). Caregivers also reported significantly more behavioral concerns in males, including internalizing behaviors ($F = 5.64$, $p = .03$), externalizing behaviors ($F = 4.73$, $p = .05$), and overall maladaptive behavior ($F = 5.45$, $p = .03$). Females generally fell at the upper end of the Average range in all three areas, whereas males were consistently in the Elevated range. (Fig. 3).

In contrast, no gender differences were found in cognitive or visuomotor functioning.

Longitudinal findings

A series of repeated measures of analysis of variance were completed to examine change over time in intellectual functioning. Two sets of analyses were completed; the first examined changes in raw scores to determine whether there were any absolute changes (i.e., intellectual development or learning), and the second examined standard or scaled scores to assess changes in relative differences (i.e., between the subjects and normative data). Change in raw scores without a corresponding change in standard scores would indicate development along a predictable trajectory, whereas change in standard scores would indicate a gain or decline in skills relative to typical patterns of development.

In overall IQ, there was significant improvement in raw scores from T1 to T2 to T3 ($F = 16.213$, $p < .001$) but not in standard scores, indicating stable overall development. In Fluid Reasoning, there was significant change evident both in raw scores ($F = 9.456$, $p = .003$) and standard scores ($F = 4.334$, $p = .034$), but the pattern of change was different; raw score change was best represented by a linear model ($F = 10.284$, $p = .015$) whereas standard score change was quadratic ($F = 20.250$, $p = .003$). Inspection of means reveals raw score gains from T1 to T2 but then a plateau in skills from T2 to T3 (see Fig 4), with the result that relative performance (standard scores) improved from mildly impaired to borderline from T1 to T2 (+0.8 SD), but then declined back to the impaired range from T2 to T3 (−0.9 SD). Significant raw score changes were evident in three of four subtests, Figure Ground ($F = 16.114$, $p < .001$), Form Completion ($F = 8.972$, $p = .003$), and Repeated Patterns ($F = 6.269$, $p = .031$, corrected via the Greenhouse-Geisser procedure for violation of sphericity). Scaled score (relative) changes were evident in two subtests, Figure Ground ($F = 13.235$, $p = .008$) and Repeated Patterns ($F = 4.607$, $p = .029$), both of which conformed to a quadratic model. Interestingly, Figure Ground raw scores (and scaled scores) declined from T1 to T2, and then increased from T2 to T3 (though the fit with a quadratic model was only slightly better than the fit with a linear model), whereas Repeated Patterns showed a profile of plateauing raw scores and increasing-then-decreasing scaled scores.

In all of these findings, there were no significant interactions with age at time of assessment, or gender.

DISCUSSION

Consistent with prior findings, the majority (78%) of participants fell within the range of Intellectual Disability. Nonverbal fluid reasoning (FR) was again found to be a relative strength, though the present data afford some additional insight into the nature of this finding. First, the advantage is specific to nonverbal FR; participants did not show a comparable advantage on verbal FR tasks. Second, the relative strength in nonverbal FR appears to decline across age groups, with the Child group performing in the low-average range, the Adolescent group falling in the mild range of disability, and the Adult group in the moderate range. This decline did not appear to be due to an actual loss of skills; instead, it reflected a plateau in the development of nonverbal FR in adolescence. The opposite trend was evident in verbal knowledge, with the Adult group performing 0.7 SDs above the Child group on the PPVT-IV, though this effect did not reach statistical significance. Nonetheless, it raises the interesting possibility that nonverbal skills may plateau around the time that accelerated development occurs in verbal skills.

In a previous report [Axelrad et al., 2007], longitudinal findings indicated that nonverbal intellectual abilities remained stable over time. In the present study, we again found stable overall IQ, but we uncovered interesting patterns in the development of nonverbal FR. Consistent with the age cohort effects discussed above, participants showed clear improvement in nonverbal FR from T1 to T2, with stability in skills evident from T2 to T3. This pattern suggests that there is something of a “late bloomer” effect with development of nonverbal FR occurring in late childhood/early adolescence, though these skills plateau subsequently.

A strength of this study compared to prior investigations was a more equal distribution of males ($n = 9$) and females ($n = 9$), allowing for examination of gender differences. The findings indicated large gender differences in caregiver-rated adaptive functioning, with females demonstrating higher functioning across all domains (Communication, Daily Living Skills, and Socialization). It is difficult to know whether these gender differences reflect true functional differences in females’ adaptive behavior, or differences in caregiver perceptions of male and female children, though it is important to note that no gender differences were found in intellectual or visuomotor functioning.

Previous reports have noted elevated levels of anxiety and other internalizing behaviors in individuals with Costello Syndrome [Axelrad et al., 2007; Kawame et al., 2003; Galera et al., 2006]. Consistent with our findings at T2 [Axelrad et al., 2007], 75% of participants had elevated or clinically-significant internalizing difficulties, whereas a slightly higher proportion had elevated externalizing problems at T3 (38% versus 27%). Interestingly, caregivers consistently noted higher maladaptive behaviors in males, with nearly equal rates of internalizing and externalizing difficulties.

These findings may guide approaches to learning at different stages of development. During late childhood/early adolescence, when individuals with Costello syndrome appear to rapidly develop nonverbal reasoning, they might benefit from an educational approach that prioritizes visual presentation of information. During adolescence, when their verbal skills appear to accelerate, they might benefit from an increasing focus on vocabulary development and verbal information presented in tandem with visual materials. Use of a Picture Exchange Communication System (PECS) [Bondy and Frost, 1994] could help bridge the gap between nonverbal and language skills and reinforce development of more

complex language [Lancioni et al., 2007]. As language skills develop further, use of more full-fledged language-based interventions such as “social stories” and “comic strip conversations” [Gray, 1998] may promote better functional communication and social skills [Ali and Frederickson, 2006]. Males might benefit from a concerted effort by parents and teachers to further independence in adaptive skills. It will be informative to follow this cohort of patients and to assess changes over time, and to further investigate interesting trends, such as strengths in social skills and difficulties with internalizing behaviors.

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Figure 1. Cognitive Ability

	Profound Mental Retardation	Severe Mental Retardation	Moderate Mental Retardation	Mild Mental Retardation
	Below 25	26-40	41-55	55-69
Leiter-R Brief IQ	0	22	28	28
Leiter-R Fluid Reasoning	0	0	44	17
Leiter-R Memory	0	0	0	43
Stanford-Binet Verbal	0	0	44	39

Figure 2. Age Effects

	Child	Adolescent	Adult
Leiter-R Brief IQ	72	55	41
Leiter-R Nonverbal Fluid Reasoning	81	64	49
VMI	63	58	45
PPVT-IV	58	64	69

Figure 3. Gender Differences in Adaptive Skills

	Communication	Daily Living Skills	Socialization
Female	73	67	77
Male	63	62	70

Figure 4. Longitudinal Pattern in Fluid Reasoning

	Time One	Time Two	Time Three
Raw Score	37	46	46
Standard Score	62	73	60

Table I

Descriptive Information for Participants

	N(males/females)	HRAS mutation	Medical Issues
Child Cohort 4–9 years old	6 (4/2)	1 p.T58I 5 p.G12S	1 Chiari 1 Malformation 2 Seizure activity
Adolescent Cohort 11–14 years old	7 (2/5)	1 p.G13C 6 p.G12S	2 Chiari 1 Malformation 1 relapsed rhabdomyosarcoma 2 VP Shunt
Adult Cohort 21–25 years old	5 (3/2)	5 p.G12S	None