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Behavioral Functioning in Cardiofaciocutaneous Syndrome: Risk Factors and Impact on Parenting Experience

Elizabeth I. Pierpont[1]* and Melinda Wolford[2]

[1]Division of Clinical Behavioral Neuroscience, Department of Pediatrics, University of Minnesota Medical School, Minneapolis, Minnesota

[2]Department of Counseling, Special Education and School Psychology, Youngstown State University, Youngstown, Ohio

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The present study is an investigation of behavioral functioning in children with cardiofaciocutaneous syndrome (CFC). CFC is a rare single-gene disorder associated with cardiac disease, characteristic skin and facial features, intellectual disability, and neurological complications such as seizures and structural brain anomalies. Emotional and behavioral features of CFC have not been systematically investigated. We aimed to identify key variables that contribute to psychopathology during childhood and adolescence, and to examine the impact of challenging behaviors on the caregiving experience. Parents of 34 children and adolescents with CFC completed standardized broadband measures of child emotional and behavioral functioning, as well as measures of sensory modulation, functional communication, and caregiver stress. Results indicate that children with CFC syndrome are at heightened risk for psychopathology, with attention problems, social difficulties, and unusual behaviors (e.g., obsessive thoughts, strange behaviors, repetitive acts) found to be especially prevalent. Behavioral challenges in children with CFC syndrome were significantly associated with a history of obstetric complications and with problems modulating sensory information. With regard to the impact of child neurocognitive and behavioral issues on the caregiving experience, parent self-reported stress was significantly higher among parents of children who engaged in more problem behaviors, and lower among parents whose children could communicate effectively with others. Results of this study suggest avenues to help families cope with CFC-related stressors and enhance overall functioning. In particular, this study highlights the need for educational and treatment interventions aimed at addressing sensory needs, increasing functional communication, and identifying and managing challenging behaviors.

Key words: cardiofaciocutanous syndrome; RASopathies; behavior; attention; social; communication; sensory processing; sensory modulation; parenting stress

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INTRODUCTION

Cardiofaciocutaneous (CFC) syndrome is a rare genetic condition characterized by congenital heart disease, craniofacial features, dermatologic and gastrointestinal abnormalities, neurocognitive delays, and seizures [Pierpont et al., 2014]. CFC belongs to a group of genetically related syndromes ("RASopathies") that are caused by gene mutations within the RAS-mitogen activated protein kinase (RAS-MAPK) signaling pathway [Rauen, 2013]. In addition to CFC, the RASopathies include Noonan syndrome, Costello syndrome, and neurofibromatosis type 1, among others. In the majority of individuals diagnosed with CFC, the disorder is caused by a sporadic mutation within the *BRAF* gene or, less frequently, within the *MEK1*, *MEK2*, or *KRAS* genes [Niihori et al., 2006; Rodriguez-Viciana et al., 2006]. An epidemiological study conducted in Japan reported an estimated prevalence of CFC at 1 in 810,000 individuals [Abe et al., 2012].

Many individuals with CFC experience significant neurological involvement, which may include seizures, macrocephaly, hypotonia, ocular-motor problems, hydrocephalus, or brain imaging anomalies [Yoon et al., 2007]. Parent surveys indicate that sleep disturbances are common, such as poor sleeping patterns, sleep apnea, and night terrors [Armour and Allanson, 2008]. While global developmental

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*Correspondence to:
Elizabeth I. Pierpont, Department of Pediatrics, University of Minnesota Medical School, Mayo Mail Code 486, 420 Delaware Street SE, Minneapolis, MN 55455.
E-mail: pier0053@umn.edu
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delays are reported to be universally present in CFC [Yoon et al., 2007; Armour and Allanson, 2008], few studies have included data obtained from standardized psychometric measures. Due to concerns related to poor visual processing, inattentiveness, and behavioral challenges, as well as the severity of developmental delay among some individuals, it can be challenging to obtain an accurate assessment of IQ in children with CFC. Estimated intellectual functioning generally ranges from mild to severe intellectual disability [Cesarini et al., 2009; Allanson et al., 2011]. Occasionally, IQs within the low average to average range have been reported in individuals with established CFC-associated mutations (i.e., in *BRAF*, *MEK1*, or *MEK2*), although many of these individuals were initially clinically diagnosed with another RASopathy such as Noonan syndrome [Koudova et al., 2009; Pierpont et al., 2009; Sarkozy et al., 2009; Allanson et al., 2011]. A recent study reported a median IQ of 39 (range: 19–80) in a group of 11 individuals with molecular confirmation of CFC [Alfieri et al., 2014].

Developmentally, gross motor delays are extremely common in CFC. Parent surveys indicate that, on average, children with CFC begin to walk independently at age 3 years, although approximately 18% of individuals are unable to attain independent walking [Yoon et al., 2007]. Language development is highly variable. Most children are able to speak in phrases or full sentences by school age, but about 9–31% remain nonverbal throughout childhood [Yoon et al., 2007; Pierpont et al., 2010b]. Caregiver adaptive behavior ratings indicate that expressive language is typically more delayed relative to receptive language [Pierpont et al., 2010b]. Many families report use of sign or alternative/assistive technologies to facilitate communication [Armour and Allanson, 2008]. A study of overall adaptive functioning in individuals with CFC aged 1–21 years reported standardized scores ranging from 27 (severe deficit) to 76 (moderately low) [Pierpont et al., 2010b]. Although longitudinal data have not been reported, cross-sectional research suggests that children and adolescents with CFC continue to gain adaptive skills over the course of development, but may exhibit more significant delays relative to peers as they grow older.

Limited information is available regarding specific behavioral features of CFC, including personality characteristics and mental health concerns. A recent study of behavior in the RASopathies, which included data from 10 individuals with CFC, reported that 50% of the CFC participants were rated in the "clinically significant" range for internalizing behaviors on the Achenbach Child Behavior Checklist, and 40% scored in the "clinically significant" range for externalizing behaviors [Alfieri et al., 2014]. Two studies utilizing parent rating scales reported that individuals with CFC demonstrated heightened risk for symptoms of autism spectrum disorder (ASD), such as challenges related to social communication and restricted or repetitive interests and behaviors [Adviento et al., 2014; Alfieri et al., 2014]. Research on other RASopathies indicates that symptoms of attention deficit hyperactivity disorder (ADHD) are also very common in this group of syndromes [e.g., Payne et al., 2011; Isenberg et al., 2013; Pierpont et al., 2015]. Additional behavioral challenges such as irritability, chronic crying, stubbornness, aggressive behaviors, and shortened attention span have been reported in CFC [Armour and Allanson, 2008], although up to this point, there has been no research to identify underlying factors that may drive these behaviors. Research on children with other developmental disabilities such as ASD and ADHD suggests that emotional and behavioral challenges may be linked to sensory processing dysfunction [Mangeot et al., 2001; Tomchek and Dunn, 2007] or to expressive communication challenges [Snowling et al., 2006; Hartley et al., 2008]. Nevertheless, little research is available to understand the impact that medical, sensory, or communication challenges have on social-emotional functioning in individuals with CFC.

The current study reports on an international cohort of 34 children and adolescents with CFC syndrome (16 females, 18 males). The goals of the study were to (i) obtain an improved characterization of behavioral features associated with CFC in a relatively large sample of individuals with this rare syndrome; (ii) identify key medical and developmental factors associated with behavioral outcomes; and (iii) investigate the contributions of behavioral and communication challenges to caregiving stress among parents of children with CFC.

MATERIALS AND METHODS

Participants

Study participants were recruited at the 2013 meeting of the CFC family advocacy and support group (CFC International), as well as via study postings on the CFC International email listserv. Parents of individuals with CFC between the ages of 6 and 18 years (mean age = 11.04 years, SD = 3.46 years) were invited to participate. A total of 34 children and adolescents with CFC were enrolled in the study, including two sets of CFC twins. Study enrollment was limited to individuals with confirmed CFC gene mutations. The cohort was comprised of 26 individuals with *BRAF* mutations, 4 individuals with *MEK1* mutations, 3 individuals with *MEK2* mutations, and 1 individual with a *KRAS* mutation. Families originated from the following countries: United States, Canada, Iceland, France, Germany, Austria, United Kingdom, Ireland, and Australia.

As expected, significant medical and neurological involvement was reported in our sample of individuals with CFC. Obstetric complications were common (74%), including conditions such as polyhydramnios (excess amniotic fluid), gestational diabetes, poor maternal weight gain, pre-eclampsia/eclampsia, preterm birth (<37 weeks gestation), and neonatal respiratory distress. Fifteen children (44%) had a history of seizures, the majority of whom (n = 13) were currently taking medications for seizure management. Seizures were difficult to control in some cases, as 7 of these 15 patients (47%) had reportedly experienced more than one seizure during the past year. Cardiac disease, though often mild, was present in 62% of the children with CFC. Significant gastrointestinal/feeding problems were reported in 56% of individuals, including history of gastrointestinal surgeries, use of a feeding tube, inability to chew solid foods, severe reflux, or aspiration of foods/liquids. Current or past use of pharmacotherapies for behavioral issues was reported for eight children (24%). These included stimulant and non-stimulant medications to improve attention (15%), antidepressants prescribed for anxiety (6%), and antipsychotic medication (e.g., risperidone) to manage irritability/outbursts (9%).

Measures

Achenbach child behavior checklist (CBCL). Parents of individuals with CFC completed the CBCL, a widely used and well-validated standardized caregiver response questionnaire that assesses behavioral and emotional problems in children ages 6–18 years [Achenbach and Rescorla, 2001]. A caregiver rates the child's behaviors using the following format: 0 (not true), 1 (somewhat or sometimes true), or 2 (very true or often true). The CBCL includes eight syndrome scales measuring the following symptoms: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior. The eight syndrome scales can be summarized into three broader scales: internalizing (anxious/depressed, withdrawn/depressed, somatic complaints), externalizing (rule-breaking behavior, aggressive behavior), and total problems score.

Although the CBCL was not originally developed for children with cognitive impairments, this instrument has established validity for use with individuals with mild to moderate intellectual disability [Dekker et al., 2002; Koskentausta et al., 2004], and has been previously used to study genetic syndromes associated with significant neurological involvement [e.g., Graham et al., 2005], including other RASopathies [Denayer et al., 2011; Pierpont et al., 2015].

Short sensory profile (SSP). The SSP is a 38-item caregiver questionnaire that identifies a child's sensory processing behaviors pertaining to seven domains: tactile sensitivity, taste/smell sensitivity, movement sensitivity, underresponsive/seeks sensation, auditory filtering, low energy/weak, and visual/auditory sensitivity [Dunn, 1999]. Items are scored on a 5-point Likert scale ranging from "always" to "never." The SSP yields raw scores and classification categories (typical sensory modulation, probable difference, and definite difference). Lower raw scores reflect more sensory modulation concerns. The total score is reported to be the best indicator of overall sensory modulation difficulties [Dunn, 1999]. The SSP has strong psychometric properties, including good internal consistency of subscales (ranging from 0.70 to 0.90) and discriminant validity in identifying children with and without sensory modulation dysfunction [McIntosh et al., 1999].

Functional communication classification system (FCCS). The FCCS is a caregiver report measure designed to reflect the level of functional communicative participation among children with varying degrees of speech/language impairment [Barty and Caynes, 2009]. Unlike most standardized tests of speech and language, the FCCS is appropriate for individuals with very poor speech intelligibility or those who use alternative or augmentative communication methods. The FCCS evaluates the effectiveness of everyday communication (i.e., how well an individual can communicate a message to familiar and unfamiliar communication partners) rather than performance of specific speech/language competencies. In the FCCS, children are classified among one of five levels (Table I) according to the degree of functional communication they demonstrate in daily life. Children who are classified at Level I will have minimal or no difficulties with communication as compared to typically developing peers, whereas children at Level V primarily communicate unintentionally with other through their movements and behavior. Ratings on the FCCS have been shown to be strongly associated with measures of motor speech impairment as well as with other rating scales assessing functional communication [Mei et al., 2014].

TABLE I. Parent Ratings Using the Functional Communication Classification System (FCCS) in 34 Children and Adolescents With CFC Syndrome

Measure	n (%)
I. An effective communicator in most situations.	2 (6)
II. An effective communicator in most situations, but does need some help.	11 (32)
III. An effective communicator in some situations. Can communicate a range of messages/topics to most familiar people.	9 (26)
IV. Assistance is required in most situations, especially with unfamiliar people and environments. Communicates daily/routine needs and wants with familiar people.	9 (26)
V. Communicates unintentionally with others, using movement and behavior.	3 (9)

Pediatric inventory for parents (PIP). The PIP is a 42-item self-report measure of parenting stress associated with caring for a child with a medical illness. Items on the PIP describe events associated with caregiving for a medically complex child, grouped into one of four domain subscales (communication, medical care, role functioning, and emotional functioning). Items are rated based on (i) the frequency of event (ranging from "never" to "very often") and (ii) the difficulty/distress the parent experiences related to the event (ranging from "not at all difficult" to "extremely difficult"). Higher scores indicate higher frequency and stressfulness. The PIP has excellent internal consistency reliability and construct validity, and is demonstrated to correlate with other measures that assess state anxiety and parenting stress [Streisand et al., 2001]. It has been utilized to identify challenging aspects of the parenting experience for individuals with other genetic syndrome associated with significant physical health and cognitive challenges [e.g., Storch et al., 2009; Grant et al., 2013].

Procedures

The research protocol was approved by the University of Minnesota Institutional Review Board, and informed consent was obtained from all study participants (parents of children with CFC) prior to enrollment. Participants completed the study questionnaires either at the 2013 CFC International meeting in Orlando, FL ($n = 19$) or by returning study packets sent through the mail ($n = 15$). In addition to the study questionnaires, parents also completed a demographic form to obtain information about the child's age, developmental and medical history, and family characteristics.

Statistical Analysis

Data analysis was performed using the IBM SPSS Statistics 23 package. Complete data on all measures were available for 32

participants. Subscale and total scores were unavailable for one participant on the SSP and for one participant on the PIP, due to missing responses for some items. Given the small number of missing scores, listwise deletion was used for analyses that included these measures.

Descriptive statistics are reported for the behavioral measures. The CBCL test manual recommends that raw scores be utilized when the syndrome scales are included in statistical analyses, as *T*-scores for these scales are truncated at <50 [Achenbach and Rescorla, 2001]. In order to account for age and sex differences and to preserve all the differentiation of scores, raw scores obtained for children with CFC on the CBCL were converted to *z*-scores for each of the syndrome scales using published normative data for each child's sex and age [Achenbach and Rescorla, 2001]. Higher *z*-scores are indicative of greater problems (Table II). *T*-scores (mean = 50, SD = 10) for the internalizing, externalizing, and total problems (problem behavior summary scales) are not truncated and are reported in Table II. As defined in the CBCL manual, threshold scores for clinically significant scores were defined as *T*-score > 63 for the problem behavior summary scales and *T*-score > 69 for each of the syndrome scales [Achenbach and Rescorla, 2001].

In order to test the potential effect of medical variables on behavioral functioning, *t*-tests were used to compare children with and without each medical risk factor with regard to behavioral functioning. A Holm–Bonferroni correction [Holm, 1979] was applied to adjust for multiple comparisons. Linear regression analysis was performed to assess the association between scores on the key predictor variables (sensory modulation scores, functional communication, and obstetric complications) and behavioral functioning. Continuous predictors (sensory modulation and functional communication) were centered on the median score for that measure. A binary indicator of perinatal risk (coded: obstetric complications reported = 1, no obstetric complications reported = 0) was included in the regression model. Follow-up correlations were conducted to examine the relationships between modalities of sensory processing and CBCL behavior scales.

Regression analysis was used to examine whether child medical and behavioral characteristics contributed to parenting stress in CFC families. An index of medical severity was calculated based on the number of the following medical/neurological complications a child experienced: cardiac disease, seizures, obstetric complications, GI/feeding difficulties. Scores ranged from 0 (none of these complications) to 4 (all). This medical severity index was strongly correlated with the sum of the frequency items from the medical care index on the PIP ($r = 0.61$, $P < 0.001$), indicating that these scales measured a similar construct. The regression model included the medical severity measure, functional communication, and total behavior problems as predictors of parenting stress levels. Total score on the difficulty scale of the PIP was used as the outcome measure, as this scale indexes the level of experienced stress ("How difficult is this experience for you"?) of parents within the caregiving context. Pearson correlations between subscales of the CBCL, the FCCS, and PIP subdomains were also examined. All reported tests were two-tailed.

RESULTS

Sensory Modulation

The vast majority of children with CFC (28 participants; 85%) were classified as having "definite" sensory modulation issues based on their SSP total score. One child (3%) was classified as having "probable" sensory processing issues, and four children (12%) were classified as having overall "typical performance" on the SSP. Classification of children with CFC on each of the seven subscales of

TABLE II. Parent Ratings of Problem Behaviors in Children With CFC Syndrome, Based on Gene Mutation

	Mean (SD)					
CBCL scales	*BRAF* (n = 26)	*MEK1* (n = 4)	*MEK2* (n = 3)	*KRAS* (n = 1)	Full sample (n = 34)	Clinically elevated in full sample[a] (%)
Problem behaviors (*T*-scores)						
Internalizing	61.31 (9.64)	54.00 (9.56)	45.00 (10.44)	61	59.00 (10.51)	29
Externalizing	58.03 (7.25)	45.25 (2.50)	42.67 (15.89)	61	55.26 (9.45)	21
Total problems	64.77 (7.51)	54.75 (6.55)	50.33 (13.05)	62	62.24 (9.04)	50
Syndrome scales (*z*-scores)						
Anxious/depressed	0.61 (1.38)	−0.24 (0.45)	−1.03 (0.07)	0.62	0.36 (1.32)	6
Withdrawn/depressed	1.29 (1.83)	−0.19 (0.73)	−0.13 (0.66)	−0.24	0.95 (1.74)	12
Somatic complaints	2.10 (2.26)	1.67 (2.10)	0.28 (0.96)	2.18	1.89 (2.15)	29
Social problems	1.82 (1.35)	0.25 (0.57)	0.35 (1.42)	0.54	1.47 (1.40)	18
Thought problems	3.05 (2.10)	1.63 (1.54)	0.33 (1.75)	1.83	2.60 (2.12)	44
Attention problems	2.14 (1.00)	1.43 (1.19)	0.87 (1.87)	1.23	1.92 (1.13)	47
Rule-breaking behavior	−0.17 (0.73)	−0.68 (0.41)	−0.68 (0.38)	0.22	−0.26 (0.69)	3
Aggressive behavior	1.11 (1.11)	−0.56 (0.04)	−0.14 (1.62)	1.51	0.82 (1.22)	9

[a]Clinically elevated scores are defined as *T*-score > 63 for the problem behavior summary scales and *T*-score > 69 for each of the syndrome scales.

the SSP are depicted in Figure 1. Greater than 75% of the children with CFC were reported to experience significant abnormalities with regard to sensation-seeking behaviors (e.g., seeks noise or movement, touches objects and people, jumps from one activity to another) and weakness/low energy (e.g., poor endurance, tires easily, has weak grasp). Additionally, more than half of children with CFC had significant differences from the normative sample on scales measuring tactile sensitivity, visual/auditory sensitivity, and auditory filtering (which refers to the ability of the child to attend to important auditory input while filtering out distractions).

Functional Communication

Functional communication challenges were common in this cohort (Table I). Our results indicate that over one-third of children with CFC (35%) either have very minimal intentional communication capability or struggle to communicate messages other than basic needs and desires. The remaining participants were able to communicate a wider variety of messages to a broader audience, but many children did require help, especially when communicating with unfamiliar people. Only 6% of children with CFC were reported to be an effective communicator about a range of topics without any assistance.

Behavioral Functioning

Results from the CBCL indicate that 50% of the children with CFC were rated within the clinically significant range with regard to total problems (Table II). The mean CBCL score for children with CFC was significantly higher than the normative sample, mean difference = 12.24 (95% confidence interval [CI]: 9.08–15.38), one-sample *t*-test, $t_{33} = 7.90$, $P < 0.001$. While girls with CFC tended to have somewhat fewer overall behavioral challenges than boys with CFC, this difference was not significant in this sample, mean difference = −4.69 (95%CI: −10.89 to 1.50), $t_{32} = -1.50$, $P = 0.13$. To examine whether behavioral problems differed based on the age of participants in the study, the CBCL Total Problems scale was compared for children (ages 6–11) and adolescents (ages 12–18). This test yielded no significant difference between the younger and older subgroups, mean difference = −2.98 (95%CI: −9.61 to 3.64), $t_{32} = -0.92$, $P = 0.37$. Correlations between participant chronological age and each of the CBCL subscales were also examined, and none were found to be significant.

Clinically significant internalizing behaviors were evident in 29% of the participants, with withdrawn behaviors exhibited more frequently than anxious behaviors, particularly among children with *BRAF* mutations. Clinically significant externalizing behaviors were evident in 21% of the sample. When examining each of the specific syndrome scales individually, the greatest differences between individuals with CFC and the normative sample (>1 SD) were seen on the somatic symptoms, social problems, thought problems, and attention problems subscales. The latter three subscales do not contribute to the internalizing or externalizing problem scales. An item analysis indicated that 11 items on the CBCL were very frequently endorsed (receiving an average rating across all participants with CFC of >1.0). These included five items related to attention difficulties (acts too young for his/her age; fails to finish things he/she starts; cannot concentrate/pay attention for long; cannot sit still, restless, or hyperactive; inattentive or easily distracted). The remaining six items indicated concerns related to repetitive thinking or behaviors (repeats certain acts over and over; cannot get his/her mind of certain thoughts), sleep problems (trouble sleeping), motor or speech delays (poorly

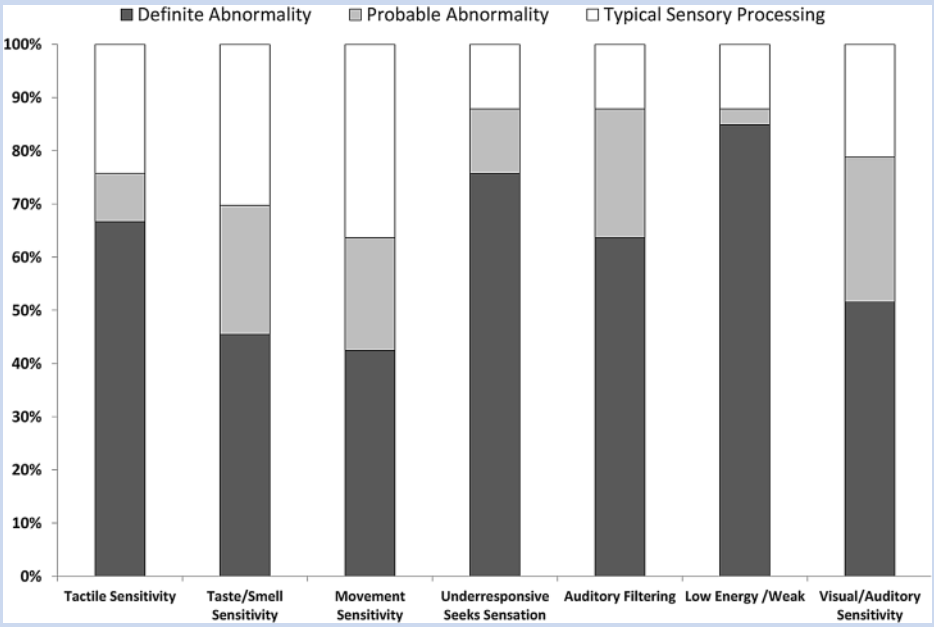

FIG. 1. Sensory modulation classifications of children with CFC on the short sensory profile.

coordinated or clumsy; speech problem), and caregiver-dependence (demands a lot of attention).

Risk Factors for Behavioral Difficulties

It was hypothesized that greater medical and neurological severity could impact a child's behavioral trajectory. Therefore, as a first step, we examined whether presence or absence of each of four medical variables (seizure history, cardiac disease, obstetric complications, GI/feeding issues) was related to increased behavior challenges in CFC. After adjusting for multiple comparisons, only one of these variables was found to be significantly related to CBCL total problems score. Children who experienced significant pre- or perinatal complications exhibited greater overall behavioral challenges than those who did not experience obstetric risk factors, mean difference = 9.24 (95%CI: 2.78–15.70), $t_{32} = 2.91$, $P = 0.006$.

In order to examine the relative contributions of medical and developmental variables to behavioral outcomes, a regression analysis was conducted. Functional communication (FCC score), sensory modulation (SSP total score), and history of obstetric complications were entered as predictors of CBCL total score (Table III). Perinatal risk was significantly associated with behavioral difficulties, with obstetric complications predicting an 8-point increase in CBCL scores. Problems with sensory modulation also predicted behavioral outcomes. Lower scores on the SSP (indicating greater sensory processing difficulties) were associated with increased behavioral challenges. Level of functional communication was not predictive of overall behavior problems in this sample.

To further explore the relationship between sensory modulation difficulties and behavioral difficulties, bivariate correlations between each of the modalities of sensory processing measured by the SSP and the internalizing and externalizing scales of the CBCL were examined (Table IV). Because sensory processing problems are known to be associated with attention and social difficulties in other populations [Mangeot et al., 2001; Tseng et al., 2011], the attention problems and social problems subscales were also included (items from these scales are not included in the internalizing or externalizing scales). Internalizing behaviors were correlated with several modalities of sensory processing, including sensory sensitivities (e.g., visual/auditory sensitivity, tactile sensitivity), auditory filtering, and low energy/poor strength. Individuals with greater sensory processing difficulties in these areas exhibited more internalizing (e.g., anxious, withdrawn) behaviors. In contrast, externalizing behaviors were most closely correlated with the sensation-seeking aspect of sensory processing. Attention and social problems were associated with both over- and under-responsivity to sensory stimuli.

Parenting Stress in CFC Families

An item analysis of the PIP enabled a view into which caregiving experiences were most frequent and most stressful for parents of children with CFC. With regard to the most frequent experiences, nine items received an average rating >3.0 on a 5-point Likert scale for the frequency scale. These items indicated that parents of children with CFC frequently experience the following events in their daily lives: duties related to medical caregiving ("Helping my child with medical procedures;" "Helping my child with his/her hygiene needs"), concerns about their child ("Worrying about the long her impact of the illness;" "Feeling helpless about my child's condition;" "Feeling uncertain about the future;" "Seeing my child's mood change quickly"), concerns related to managing their family's needs ("Trying to attend to the needs of other family members") and disruption of their own self-care needs ("Difficulty sleeping;" "Having little time to take care of my own needs"). Item analysis of the PIP revealed several experiences which parents of children with CFC found particularly difficult or stressful; six items received and average score >3.0 on the difficulty scale. These experiences included worries about their child's well-being ("Knowing my child is hurting or in pain;" "Thinking about my child being isolated from others;" "Feeling helpless over my child's condition;" "Feeling scared that my child could get very sick or die") and concern about the future ("Worrying about the long-term impact of the illness;" "Feeling uncertain about the future").

To determine which child medical and behavioral variables were most associated with parenting stress, a regression analysis was conducted. Child medical severity, functional communication (FCCS), and challenging behaviors (CBCL total problems) were entered as predictors of the total PIP difficulty scale. Parenting stress among caregivers of a child with CFC was significantly higher for parents of children with more limited functional communication and children with greater overall problem behaviors (Table V).

Finally, in order to better characterize associations between child behavior and communication concerns and parenting stress, we examined correlations between FCCS and CBCL subscale scores and parent-reported stress within each domain of the PIP (Table VI). Parents of children who had more limited functional communication skills (i.e., higher FCCS scores) reported higher levels of stress within all domains. Child behavior problems were

TABLE III. Results of Regression Model Predicting Behavioral Functioning (CBCL Total Problems Score) Based on Medical and Developmental Variables

Model	Regression coefficient (B)	95%CI for B	t	P	Adjusted R^2
Intercept	56.49	51.21 to 61.75			0.32
Obstetric complications	8.29	2.12 to 14.45	2.75	0.010	
Functional communication (FCCS)	−0.78	−3.77 to 2.21	−0.54	0.597	
Sensory modulation (SSP)	−0.17	−0.30 to −0.04	−2.76	0.010	

TABLE IV. Pearson Correlations (r) for Relationships Between Sensory Modulation Domains and Behavioral Challenges in 33 Children With CFC Syndrome

Short sensory profile subscale	Internalizing behaviors	Externalizing behaviors	Attention problems	Social problems
Tactile sensitivity	−0.41*	−0.11	−0.40*	−0.38*
Taste/smell sensitivity	−0.15	0.04	−0.18	0.05
Movement sensitivity	−0.24	0.13	−0.04	−0.01
Underresponsive/seeks sensation	−0.33	−0.46**	−0.52**	−0.43*
Auditory filtering	−0.42*	−0.30	−0.68**	−0.43*
Low energy/weak	−0.35*	0.12	−0.24	−0.18
Visual/auditory sensitivity	−0.38*	−0.23	−0.51**	−0.35*

*$P < 0.05$.
**$P < 0.01$, two-tailed.

not associated with increased stress related to medical care aspects of parenting (e.g., making decisions about medical care, performing or watching procedures), but these problems were strongly associated with stress surrounding communicating with others (e.g., arguing with family members, disagreements with others, absorbing medical information, talking with clinicians). Additionally, child internalizing behaviors and attention problems were related with multiple facets of parent stress. Parents of children with more internalizing and attention problems reported greater difficulty in communicating with others, more intense emotional reactions to events (e.g., feelings of uncertainty, helplessness, numbness, worries) and greater stress surrounding role changes related to caregiving demands (e.g., struggling to maintain work, having little time to care for one's self or other family members, changes in the partner/spouse relationship).

DISCUSSION

In order for medical providers to make appropriate recommendations to assist families of children with disabilities in navigating the educational and mental health care systems, it is essential to obtain knowledge of the range behavioral features that can be associated with the child's diagnosis. Unfortunately, for many rare syndromes like CFC syndrome, a lack of published data on neurobehavioral outcomes impedes this effort. Previous research has established that CFC is associated with mild to profound cognitive and functional disabilities which can considerably impact mobility, expressive communication and socialization [Cesarini et al., 2009; Pierpont et al., 2010b; Johnson et al., 2015]. A primary goal of the present study was to identify and analyze common behavioral issues associated CFC, and to distinguish key factors contributing to risk and resilience among children and their families. Based on research from other genetic syndromes associated with intellectual disability [e.g., Smith et al., 2012] and other RASopathies [Kayl and Moore, 2000; Alfieri et al., 2014], we hypothesized that children with CFC would exhibit heightened emotional and behavioral challenges relative to the normative population. We also expected that factors such as greater medical severity, sensory processing difficulties, and more limited communication skills would be associated with higher incidence of challenging behaviors among individuals with this diagnosis.

Only one previous study has reported data from standardized broadband measures of emotional/behavioral functioning in CFC. Alfieri et al. [2014] reported clinically significant problem behaviors in 8 out of 10 (80%) individuals with confirmed CFC mutations. Compared to the cohort described by Alfieri and coworkers, participants in our study showed a lower prevalence of clinically significant internalizing behaviors (29% in our study vs. 50% in their sample) and externalizing behaviors (21% vs. 40%). Differences in sample size and recruitment methods (i.e., clinic-based enrollment vs. recruitment through advocacy groups) may have contributed to these differences. Nevertheless, both studies found a higher frequency of problem behaviors among children with CFC than is present in the general population. This finding is consistent with research studies reporting a 3–7 times higher prevalence of psychopathology in children and adolescents with intellectual disability as compared to typically developing individuals [de Ruiter et al., 2007].

TABLE V. Results of Regression Model Predicting Caregiving Stress (Total PIP Difficulty Scale) Based on Child Medical and Behavioral Variables

Model	Regression coefficient (B)	95%CI for B	t	P	Adjusted R^2
Intercept	108.86	89.87 to 128.14			0.52
Medical severity (# complications)	−3.38	−10.99 to 4.24	−0.91	0.372	
Functional communication (FCCS)	16.99	9.26 to 24.71	4.50	<0.001	
Behavior problems (CBCL)	1.16	0.33 to 1.99	2.85	0.008	

TABLE VI. Pearson Correlations (r) for Associations Between Child Behavioral Challenges (CBCL Subscales) and Domains of Caregiving Stress (PIP Difficulty Scales)

	Communication	Medical care	Emotional distance	Role functioning
FCCS				
Functional communication rating	0.56*	0.70*	0.59*	0.48*
CBCL				
Internalizing behaviors	0.55*	0.18	0.53*	0.41**
Externalizing behaviors	0.39**	−0.05	0.28	0.18
Attention problems	0.44**	0.30	0.48*	0.51*
Social problems	0.46*	0.13	0.31	0.27

*$P < 0.01$, two-tailed.
**$P < 0.05$.

Preliminary gender-based analyses in our sample did not reveal significant differences in the rate of behavioral issues reported for girls and boys with CFC. Similarly, no noticeable age-related changes in behavioral profile were observed in this cross-sectional sample. Given the striking individual variation in neurodevelopmental findings in CFC, longitudinal data may be required to determine whether affected children exhibit shifts in the nature and severity of behavioral problems throughout childhood and adolescence, and to identify what factors drive these changes.

In terms of identifying predictors of behavioral concerns in children with CFC, two key factors emerged as predominant correlates of behavior in our analyses. First, children within our cohort who experienced perinatal complications such as preterm birth, poor maternal weight gain, pre-eclampsia, or neonatal respiratory distress were at heightened risk for behavioral difficulties relative to those who did not. This finding is somewhat unsurprising given the voluminous research literature linking neurocognitive delays to a wide variety of pregnancy and birth complications [e.g., Spinillo et al., 2009; Mackay et al., 2013]. Further research using more detailed analysis of birth records (which were not available for the current study) could delineate whether particular types of obstetric complications pose the greatest risk for later neurobehavioral concerns. Notably, we conclude from our research that obstetric complications may confer significant neurobehavioral risk in this population, however, it is also important to note that pre- and perinatal findings can be an important clue in establishing a CFC diagnosis during the neonatal period. Recognition of perinatal findings associated with CFC among physicians may allow for earlier diagnosis and better monitoring and intervention for the medical and neurological complications associated with CFC [Myers et al., 2014; Wong Ramsey et al., 2014]. This in turn would be expected to facilitate a more comprehensive and coordinated plan of care after birth that adheres to established guidelines [Pierpont et al., 2014] and results in better health and developmental outcomes.

Another key finding of the present study is the robust association between emotional and behavioral challenges and sensory modulation difficulties (i.e., difficulties organizing and regulating responses to sensory input) among individuals with CFC. In previously published studies, parents of children with CFC reported observing tactile defensiveness in their children [Armour and Allanson, 2008], but it has not previously been clear the extent to which sensory processing difficulties are related to behavioral challenges. Research on other populations has shown that challenges with sensory modulation are common in a variety of disorders that affect neurological development. Atypical sensory modulation has been reported in children with genetic syndromes like fragile X syndrome [Baranek et al., 2008] and Williams syndrome [John and Mervis, 2010], as well as complex neurodevelopmental conditions such as autism spectrum disorder [Tseng et al., 2011] and attention deficit hyperactivity disorder [Mangeot et al., 2001]. There is increasing evidence that sensory processing impairments are linked to abnormal neurophysiological responses and patterns of cortical connectivity [Davies and Gavin, 2007; Cascio, 2010]. Our research suggests that among children and adolescents with CFC, atypical sensory modulation is closely linked with emotional and behavioral problems such as social withdrawal, distractibility, and irritability. This finding suggests that sensory processing problems could be a plausible cause for some problem behaviors. Perhaps equally plausible is the possibility that problems with sensory modulation and problems with regulation of emotions/behavior arise from a common source (e.g., neurological immaturity). In either case, our results highlight the importance of addressing atypical modulation of sensory information in educational and therapeutic settings (see further discussion below).

Contrary to our initial hypothesis, functional communication abilities of children with CFC were not measurably associated with behavior challenges. Some researchers have theorized that problem behaviors among language-impaired children may arise as a result of frustration in not being able to effectively express their wants and needs [Qi and Kaiser, 2004]. Robust research exists demonstrating that problem behaviors are more common among children with language disabilities than children with age-appropriate language development [Noterdaeme and Amorosa, 1999; Charman et al., 2015]. Based on this research, we expected that children with CFC who had greater functional communication challenges would exhibit more problem behaviors, but this hypothesis was not borne out by the data. There are a number of potential explanations for the lack of association between communication skills and behavioral challenges in our cohort. One possibility is that the behaviors measured by the CBCL may not adequately capture the types of

behaviors that are most common in children with CFC who have significant cognitive and language impairments. For example, a few of the items on the CBCL do require some level of verbal communication in order to be pertinent to the child (e.g., "complains of loneliness;" "argues a lot"). Although these behaviors would have been more commonly reported among children with higher language function, the inclusion of these items would have made it difficult to detect a relationship between challenging behaviors and communication difficulties, if such a relationship does indeed exist.

In order to delve beyond the broadband composite scales (e.g., internalizing, externalizing, and total problems), we also examined parent ratings for each of the CBCL clinical subscales. Notably, parent ratings of nearly half of the children in our sample indicated clinically significant concerns on the attention problems scale, consistent with other recent studies using this instrument to measure behavior in children with RASopathies [Alfieri et al., 2014; Pierpont et al., 2015]. The attention problems scale measures problems such as poor concentration, being too active, impulsiveness, and problems completing tasks. These ADHD-like symptoms are often described to be a prominent aspect of the behavioral presentation of children with intellectual disabilities [Matson and Shoemaker, 2011]. In our sample, several children (15%) had been prescribed medication to improve focus/attention. Based on these findings, we conclude that identifying effective ways to address symptoms of inattention and hyperactivity among children with CFC is an important challenge warranting further study.

Children in our study also experienced increased risk for symptoms measured by the thought problems and social problems subscales of the CBCL. The thought problems scale consists of items assessing difficulties related to obsessive thoughts, repetitive acts, sleep problems, and strange/unusual behaviors. These behaviors are commonly reported in children with autism spectrum disorders and in intellectual disability syndromes such as Down syndrome [Mazefsky et al., 2011; van Gameren-Oosterom et al., 2013]. The social problems subscale measures concerns including difficulty maintaining age-appropriate behavior, loneliness, problems getting along with others, and being dependent on adults. Because some items on this scale may be more reflective of neurological immaturity (e.g., "poorly coordinated or clumsy;" "speech problems") rather than degree of social relatedness, elevations on this scale may actually be more reflective of the functional disabilities of children with CFC rather than issues with interpersonal motivation or relatedness per se. Nevertheless, it is intriguing to note that a similar pattern of elevations on the above-mentioned scales (social, attention, and thought problems) has been demonstrated on multiple independent samples of children with ASD [Bolte et al., 1999; Mazefsky et al., 2011]. This finding is noteworthy in light of recent studies suggesting a higher incidence of ASD traits in individuals with RASopathy syndromes [Garg et al., 2013; Adviento et al., 2014; Alfieri et al., 2014]. A profile of elevations on these scales has also been reported for children with fragile X syndrome, a genetic disorder that is associated with increased risk for ASD [Hatton et al., 2002]. These similarities in symptom presentation suggest that behavioral treatment modalities designed for children with ASD may also be applicable for some children with CFC.

Intriguing questions remain regarding the social and interpersonal experiences of children with CFC. As we noted above, many items on the social problems scale of the CBCL may be more reflective of how a child's disability affects their peer relationships rather than how interested and engaged they are in their social world. As a result, there are limitations in our ability to draw broad conclusions about the social phenotype of children with CFC from parents' responses on this scale. There is some evidence from prior research to suggest that many children with CFC and other RASopathies may exhibit deficits in social functioning that are characteristic of ASD. Adviento et al. [2014] reported results from a relatively large cohort ($n = 54$) of children with CFC whose parents were administered two widely-used autism screening measures. In their sample, 54% of children with CFC scored above a conventional threshold on the social communication questionnaire (SCQ) [Rutter et al., 2003], indicating substantially increased risk for ASD. Importantly, however, screening measures such as the SCQ tend to demonstrate lower specificity and an increase in "false positives" for children with lower IQ [Eaves et al., 2006], and the validity of these instruments for identifying ASD risk in children with severe-profound intellectual disability is less well-established than for other groups [Norris and Lecavalier, 2010]. Although restrictive and repetitive interests and behaviors are characteristic of children with ASD, they are also seen in children with cognitive disabilities and sensory issues such as those commonly experienced by children with CFC [de Vaan et al., 2016; Oakes et al., 2016]. Furthermore, data from adaptive behavior ratings of individuals with CFC suggest that social skills are similarly impacted relative to other domains such as communication and daily living skills [Pierpont et al., 2010b] and do not necessarily constitute an area of weakness in the overall profile. Additional research and clinical measurement using gold-standard ASD diagnostic assessments and other measures of social functioning (e.g., observational methods, experimental tasks) would provide key insights regarding social competencies and challenges faced by children with CFC. Critically, given the implications an ASD diagnosis has for conceptualizing a child's behavior and developing behavioral and therapeutic strategies, an individualized approach to assessment of social competencies will be important in clinical evaluations that are used to develop therapeutic recommendations.

Comparison With Other RASopathies

A comparison of results from the current study with previously published research on other RASopathies indicates both commonalities and differences in behavioral characteristics of children with CFC and those of children with Costello and Noonan syndromes. These two syndromes have highly overlapping features with CFC and are the primary differential diagnoses. Costello syndrome is caused by mutations in the *HRAS* gene and is associated with coarse facial features, feeding and growth problems, abnormalities of the heart, skin and musculoskeletal systems, increased risk for malignant tumors, and intellectual disability [Quezada and Gripp, 2007]. A few studies have used the CBCL to examine the frequency of problem behaviors in individuals with Costello syndrome. Whereas the percentage of children with Costello syndrome who were rated in these studies as exhibiting clinically significant

internalizing behaviors (6–30%) is similar to the rate among children with CFC in our sample, the rate of externalizing behaviors (6–10%) appears to be slightly lower among individuals with Costello syndrome [Axelrad et al., 2004; Alfieri et al., 2014]. Shyness, hypersensitivity, and irritability have been described as prominent behavioral concerns in children with Costello syndrome [Kawame et al., 2003], although these symptoms are most common during infancy and become less apparent as children get older [Galera et al., 2006]. Significant separation anxiety has been noted in 39% of patients with Costello syndrome [Axelrad et al., 2011]. Among older children with Costello syndrome, social interest and social functioning is noted to be an area of strength relative to other aspects of intellectual and adaptive functioning [Kawame et al., 2003; Axelrad et al., 2007, 2011].

Noonan syndrome is a relatively common RASopathy characterized by short stature, congenital heart disease, chest deformity, facial dysmorphology, and other comorbidities [Romano et al., 2010]. Children with Noonan syndrome are less likely to have cognitive disabilities relative to children with CFC [Cesarini et al., 2009]. The available research on emotional and behavioral functioning suggests that rates of clinically significant internalizing and externalizing behaviors (reported at 40% and 32%, respectively) in Noonan syndrome may be equal or greater to the rates of these behaviors in CFC as measured by the current study [Alfieri et al., 2014]. It would be reasonable to hypothesize that less severe functional disability in Noonan syndrome would explain a higher frequency of problem behaviors that depend on communication or independent mobility (e.g., expressing worries, lying, or getting into physical fights). Notably, like in CFC syndrome, problems with attention skills and social skills are some of the most commonly reported behavioral challenges in Noonan syndrome [Wood et al., 1995; Pierpont et al., 2015].

At present, it is unclear as to whether the same molecular and neurodevelopmental mechanisms contribute to psychopathology in children with different RASopathies. Some researchers have speculated that dysregulated RAS signaling does have similar downstream effects on brain and behavior across the various syndromes, such as increased susceptibility to autism spectrum traits [Adviento et al., 2014]. Nevertheless, several studies have documented wide variability in developmental and behavioral outcomes among individuals with the exact same gene mutation [Bertola et al., 2004; Pierpont et al., 2009], suggesting that child-specific medical, neurological, epigenetic, and environmental factors also play an essential role in determining outcomes. For example, it has been proposed that feeding problems and other medically related complications may contribute to excessive irritability in some children with Costello syndrome during infancy [Galera et al., 2006]. Similarly, our results suggest that sensory modulation differences, which are observed in several RASopathies [Kawame et al., 2003; Wang et al., 2005], may be a key contributor to certain behavioral patterns in CFC such as inattention, social withdrawal, or task refusal.

Importantly, it will be essential to develop a research strategy that incorporates both previously identified and novel sources of variability when interpreting results of future research studies and anticipated clinical trials targeting neurobehavioral endpoints in the RASopathies. The fact that specific medical complications in a child's history (e.g., perinatal events, feeding problems, hearing/visual problems) have been found to be associated with neurodevelopmental or behavioral outcomes in the RASopathies [Delrue et al., 2003; Pierpont et al., 2010a] suggests that these endpoints may not be immediately responsive to pharmacological interventions targeting the biochemical pathway itself. Although novel therapies do hold much excitement and promise for families, initial trials using drugs to correct cognitive and learning problems in individuals with other RASopathies (namely, neurofibromatosis type 1) have not shown significant benefit [van der Vaart et al., 2013; Rauen et al., 2015]. As such, we predict that rehabilitation therapies, educational accommodations, and behavioral interventions will continue to be a central component in addressing neurobehavioral concerns for individuals with RASopathies for some time to come.

Implications for Education and Mental Health Care

Given the increased risk for emotional and behavioral challenges identified in this study, it is recommended that periodic screening/evaluation for mental health issues should be standard of care for individuals with CFC. These evaluations should occur at diagnosis and across transitional time points in development (e.g., early childhood, school entry, adolescence, young adulthood). This recommendation is consistent with recently published guidelines regarding clinical management of CFC [Pierpont et al., 2014]. Evaluations should focus on identifying neurobehavioral strengths and weaknesses to inform treatment and educational planning. Within the context of evaluation, children who exhibit frequent challenging behaviors in the school, or other settings (e.g., withdrawal, refusal to participate, disruptive behaviors, aggressive or self-injurious behaviors) may benefit from a functional behavior assessment (FBA) to ascertain the purpose for target behaviors and enable educators and clinicians to intervene appropriately. An FBA should be individualized to address a very specific target behavior, perhaps prompting a plan to reduce the frequency or intensity of the challenging behavior or replace it with a more adaptive behavior [McKenna et al., 2015].

Results of the current study suggest that the participation of children with CFC in educational and social activities may be enhanced through interventions aimed at meeting the child's sensory needs. Thoughtful consideration of a child's responses to sensory stimuli, in combination with best practices in behavior analysis, can enable clinicians such as psychologists and occupational therapists to help parents and teachers observe, understand, and explain the sensory patterns and triggers that affect the child's behaviors. Clinicians might then support caregivers in adapting the environment to meet these needs. For example, our study found that internalizing behaviors (e.g., anxiety, withdrawal, depressed mood) were associated with a high level of sensitivity to environmental stimuli and to sensory defensiveness. This finding suggests that some children with CFC may be more apt to withdraw from their world (i.e., prefer being alone, act shy or refuse to talk, lack energy and interest) as a result of their difficulties tolerating and filtering sensory information. They may also engage in behaviors that allow them to avoid situations with high levels of sensory input (e.g., by becoming ill, engaging in self-injurious behavior, or

"shutting down"). In order to address this issue, clinicians or parents who observe anxious or withdrawn behaviors may assist the child by limiting unfamiliar or excessive sensory input in their daily lives. Another approach would be to introduce new sensory experiences in a gradual or progressive manner. For individuals with milder cognitive deficits who tend to withdraw or avoid situations, teaching more "active" coping strategies to address stressful stimuli (seeking support from others, problem-solving, engaging in a safe calming activity), may also be of great benefit [Hartley and Maclean, 2008].

Alongside a tendency to withdraw or disengage from activities, children that experience sensory hypersensitivities may be resistant to changes in their schedules and routines in order to avoid being overwhelmed with unfamiliar stimuli [Dunn, 1997]. Individuals with this profile may prefer sedentary, repetitive tasks or engage in rituals that enable them to follow familiar or preferred patterns. For these individuals, interventions that help the child to anticipate future events (i.e., to learn that situation B will often follow situation A) may reduce problem behaviors because the child will feel more secure in knowing what to expect. By establishing routines with a daily (or if necessary more frequent) sequence of predictable events, extreme emotional reactions and parent–child conflict may be significantly reduced. Notably, for children with CFC who have more limited cognitive and communication abilities, it will take longer (more exposures) for strong connections to be made. When a transition occurs or a new situation is introduced, the child may respond well to use of a visual system to track events or another type of individualized schedule [Mesibov et al., 2002]. Principles of behavior analysis can be used to develop an optimal activity schedule [O'Reilly et al., 2005]. For individuals with better language comprehension, "social stories" that provide information to fill in gaps in a child's social understanding are a promising, though not yet comprehensively evaluated, intervention that could be considered to reduce anxiety and challenging behaviors [Wright et al., 2016].

Our research suggests that taking sensory modulation concerns into account will also be an important component of care for children with CFC who exhibit externalizing behaviors (e.g., displays of temper, demanding attention, rapid mood changes, destroying property). In our sample, children with CFC syndrome who exhibited higher levels of externalizing behaviors scored higher on a scale measuring under-sensitivity to sensory input and sensory-seeking behaviors. Other research has shown that children with a sensory-seeking profile tend to engage in behaviors that increase their sensory experiences [Tseng et al., 2011], such as making constant noises, fidgeting, frequent touching or grabbing, chewing on items, or disruptive or aggressive behaviors. Dunn [1997] theorized that children engage in these types of behaviors help to meet a higher neurological threshold. For these children, enabling activities that allow for greater movement and encouraging more purposeful, creative exploration may be beneficial [Case-Smith et al., 2015]. Parent training programs for managing externalizing behaviors may also be helpful to provide support to families in how to respond to challenging behaviors [Sellinger and Elder, 2016]. In turn, this may also increase the caregivers' feeling of competency and reduce misunderstandings regarding the behaviors (e.g., incorrectly attributing a child's reaction to a situation to willful or "naughty" behavior or to poor parenting practices).

As noted above, many children with CFC experience complex combination of sensory and behavioral issues, including autistic traits [Adviento et al., 2014]. Some initial research suggests that application of evidence-based behavioral interventions can result in social and behavioral improvements for children with RASopathies who also have ASD. Alfieri et al. [2015] described a child with Costello syndrome (with accompanying severe intellectual disability and ASD traits) who participated in an evidence-based behavioral therapy program. Participation in the program was accompanied by a decrease of aberrant behavior and improvement in social interaction.

In addition to behavior assessment and intervention, biomedical interventions may be of significant benefit to some children whose emotional and behavioral concerns significantly interfere with their daily functioning and well-being. Given that many children with CFC exhibit notable ADHD symptoms (e.g., difficulties attending to tasks and maintaining focus, hyperactivity, impulsivity), use of pharmacotherapy might be indicated. Although stimulant medication has been demonstrated to be effective in treating ADHD symptoms in children with neurofibromatosis type 1 [Mautner et al., 2002; Lion-Francois et al., 2014], no studies have examined the safety or efficacy of these medications in other RASopathies. Notably, in our study, about one in six patients with CFC had received medication to address attention problems. Use of other types of psychoactive medications could be beneficial for more severe irritability or behavior problems. In light of concerns related to feeding/growth, heart disease, seizures, poor sleep, and other conditions that may affect individuals with CFC, decisions regarding medication must be made in tandem with a medical team that has full understanding of the overall health implications of these treatments for a medically and neurologically complex child.

Caregiver/Family Support

A unique component of the current study was the examination of parental emotional stress and role functioning relative to child challenging behaviors. Caregiving for a child with CFC is multifaceted, and requires varying degrees of intensity with regard to medical treatments, therapeutic interventions, and behavioral management. These caregiving demands have the potential to create heightened levels of emotional and interpersonal stress. Numerous studies have reported that parents of children with developmental disabilities are at heightened risk of experiencing psychological stress relative to parents of typically developing children, with children's problem behaviors pinpointed to be a critical contributor [Woodman et al., 2015]. Indeed, there is some evidence that among children with neurodevelopmental disabilities, parenting stress may be more related to the extent of emotional and behavior problems (e.g., hyperactivity, aggression) than to the child's severity of disability/delay [Nereo et al., 2003; Herring et al., 2006; McStay et al., 2014]. Based on this research, we hypothesized that a higher rate of problem behaviors would lead to increased parental stress in CFC families, even when accounting for the intensity of medical care necessary to address

their child's needs. Children's functional communication abilities were also examined as a possible predictor of parenting stress.

Our findings support the notion that parental stress is related to developmental and emotional challenges exhibited by some children with CFC, above and beyond than the requirements of caretaking alone. Among families enrolled in our study, medical severity of CFC did not demonstrably account for parental stress. In contrast, parenting stress was significantly higher among parents whose child struggled with functional communication. This finding is consistent with theories suggesting that the ambiguity associated with the cause of challenging behaviors may be an important contributor to parenting stress among children with sensory or behavior problems [Donenberg and Baker, 1993; Gourley et al., 2013]. For parents of children with CFC who have limited communication, there may be many potential sources of ambiguity regarding their child's behavior. Parents may feel uncertain as to what their child comprehends about a situation, what their needs are, or what their emotional experience is like. This uncertainty in turn may reduce a parent's sense of their own competence and cause increased worry or dissatisfaction in daily interactions. The finding that child communication competency was linked to parent stress levels in CFC families suggests that interventions that increase the child's ability to effectively express themselves may play a major role in making interactions more enjoyable for children and family members. Increasing a child's communicative competencies may also reduce parent worry/distress surrounding the child's ability advocate for their current and future needs, connect with others, and become more independent, which were frequently reported concerns among the parents in our study. As such, we recommend a strong focus on educational and therapeutic goals related to development of language-based competencies, including goals utilizing total communication (signs, gestures, objects, pictures, and printed as well as spoken words). Recent research suggests that use of augmentative and alternative communication strategies does not impede development of speech and may actually facilitate modest gains in speech production [Schlosser and Wendt, 2008].

Parent stress levels were also significantly associated with emotional and behavioral problems of children with CFC. In particular, child psychopathology in a variety of domains (internalizing, externalizing, attention, and social problem behaviors) was associated with higher levels of stress among parents when experiencing challenging communication scenarios (e.g., arguments/disagreements, speaking with medical providers). Furthermore, parents who rated their child as having significant attention problems or internalizing problems reported greater stress in terms of their own emotional experiences and their caregiving role. These findings highlight the importance of identification and treatment of emotional and behavioral concerns in children with CFC and similar disabilities, as these concerns significantly influence family well-being.

Furthermore, our results imply a potential positive benefit to parents from engaging with a parent support group, where they can learn about and share their experiences with various parenting or therapeutic approaches. CFC International (http://www.cfcsyndrome.org) is an important resource for information and advocacy related to CFC syndrome, and can put parents in touch with other parents of children with the same condition.

Limitations

Several limitations of this research should be noted. First, the information collected from this study was derived only from accounts parents of children with CFC. In future research, addition of perspectives from teachers/school professionals, siblings, or direct observations would enable further insights into child and family functioning. Additionally, because assessment of parental stress and child problem behaviors were both reported from the same perspective (i.e., the primary caregiver), it was not possible to obtain examine these relationships as derived from independent sources. Second, while the CBCL has been used widely to study emotional and behavioral functioning of individuals with a wide variety of neurological and genetic conditions [e.g., Dekker et al., 2002; Hartley et al., 2008; Skokauskas et al., 2012], this measure was not developed specifically for use among children with intellectual disabilities. Therefore, some items may have been less relevant in capturing the full scope of problem behaviors experienced by children with CFC, particularly among those with greater limitations in verbal expression. Third, the study design did not allow analysis of all possible factors contributing to risk/resilience in CFC families. For example, the influence of child cognitive functioning or the level of support/therapeutic resources currently utilized by the families could be investigated as potential predictors in future research. Notably, with regard to the measurement of medical severity in this study, it was not possible to quantify all of the possible medical complications in CFC given the wide variability in expression of this syndrome. Therefore, our measure focused on key variables that might be expected to impact the overall health and daily lives of patients and families. Development and validation of a more refined instrument to capture the degree of medical severity among patients with this syndrome could be a useful research tool for investigators. Finally, while the present study sample represents a relatively large cohort of children and adolescents with this rare syndrome, the size of the sample was not sufficient to conduct robust genotype–phenotype analyses.

CONCLUSIONS

The present study provides an initial analysis of problem behaviors in children with CFC and associated risk factors. It is hoped that results of our study may equip parents and clinicians with a better understanding of some of the factors influencing children's problem behaviors and the ability to manage them by modifying environmental stimulation to match children's sensory and neurological needs and/or apply evidence-based behavioral interventions. Notably, our results demonstrate the impact that communication and behavioral challenges can have on family life and parent well-being. In our study, caregiving stress was lower among parents whose children were able to communicate important messages to others (i.e., to express their wants and needs in an effective way) and was also significantly related to their child's emotional/behavioral health (i.e., whether or not they exhibited anxiety, withdrawal, aggression, and other problem behaviors). By

highlighting the impact of child characteristics on family functioning, we hope to raise greater awareness regarding the need for coordinated services to help families cope with the neurocognitive and behavioral effects of this complex syndrome. Better understanding and treatment of communication and sensory modulation difficulties will lead to improved treatment outcomes, a reduction in parental stress, and improvements in the mental health of children CFC.

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