Published in final edited form as:

J Dev Behav Pediatr. 2010 ; 31(6): 491–497. doi:10.1097/DBP.0b013e3181e2830f.

Stress Reactivity as a Moderator of Family Stress, Physical and Mental Health, and Functional Impairment for Children With Sickle Cell Disease

Marsha J. Treadwell, PhD*, Abbey Alkon, RN, PNP, PhD†, Keith C. Quirolo, MD*, and W. Thomas Boyce, MD‡

*Hematology/Oncology Department, Children's Hospital & Research Center, Oakland, CA

†Family Health Care Nursing Department, School of Nursing, University of California, San Francisco, CA

‡Human Early Learning Partnership and the Centre for Community Child Health Research, University of British Columbia, College for Interdisciplinary Studies, BC Research Institute for Children's and Women's Health, Vancouver, Canada

Abstract

Objective—To evaluate whether autonomic nervous system (ANS) reactivity modifies the relation between family stress, and physical and mental health, and functional impairment for children with sickle cell disease.

Methods—Thirty-eight 5-to 8-year old children with sickle cell disease completed a 20-minute ANS reactivity protocol measuring respiratory sinus arrhythmia and pre-ejection period during comparison and challenge tasks in social, cognitive, sensory, and emotion domains. Domain-specific reactivity was calculated as the difference between challenge and comparison tasks; overall reactivity was calculated across domains as the mean of the difference scores. ANS profile scores combined the overall respiratory sinus arrhythmia and pre-ejection period reactivity scores. Caregivers completed measures of family stress, child physical and mental health symptoms, and functional impairment.

Results—Family stress was associated with child functional impairment whereas overall and cognitive ANS reactivity was associated with co-morbid internalizing and externalizing mental health symptoms. Interaction models showed that children with the classic ANS profile (parasympathetic inhibition and sympathetic activation) in the cognitive and emotion domains were most vulnerable to the effects of stress, with more functional impairment and injuries when family stress was high, controlling for age, sex, and parent education.

Conclusion—The costs to patients and families in diminished quality of life and to the health care system could be reduced by further exploration of strategies to identify children with sickle

Address for reprints: Marsha Treadwell, PhD, Children's Hospital & Research Center Oakland, 747 52nd Street, Oakland, CA 94609; mtreadwell@mail.cho.org.

Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH.

None of the authors report any potential conflicts of interest.

cell disease who are most vulnerable under conditions of high family stress and heightened psychobiologic reactivity.

Index terms

stress reactivity; autonomic nervous system; sickle cell disease; pediatric chronic condition; child functional impairment; hemoglobinopathies

Sickle cell disease (SCD) is the second most common health disorder identified on newborn screening in the United States¹ and its complications are serious.² Although disease-related and environmental stress have been associated with exacerbations in SCD symptoms, the manifestations of SCD are highly variable.³ Strategies for determining which children with SCD are most vulnerable to experiencing negative disease outcomes can assist their health care providers in delivering coordinated, high-quality care and reducing health care costs.

In studies of stress and physical or mental health outcomes in children with SCD, a number of social and environmental factors have been examined. In a multi-site natural history study of SCD, baseline family conflict was found to increase the risk of behavior problems for 222 children aged 5 to 15 years.⁴ Another study found that positive parental psychosocial adjustment was associated with positive adaptation for children aged 5 to 16 years with SCD.⁵ Families of children and adolescents with more severe SCD clinical symptoms reported increased stress compared to those with less severe symptoms. Family cohesion and adaptability were associated with positive child psychosocial adjustment.⁶

For healthy children, interactions between physiological stress reactivity and environmental stressors are predictive of psychobiologic outcomes, such as injury, infectious illness, and behavior problems.⁷ Physiological stress reactivity in children has been assessed noninvasively using measures that reflect the autonomic nervous system (ANS) response to challenge and thus children's regulatory capacities.^{7,8} Cardiovascular measures of ANS reactivity include respiratory sinus arrhythmia, a measure of parasympathetic nervous system (PNS) response, and pre-ejection period, an index of sympathetic nervous system (SNS) activity. In one study, highly reactive children aged 3 to 5 years had the highest incidence of illnesses in the context of high stress using combined measures of SNS and PNS reactivity.⁹ Six- and 7-year-old children who had high levels of externalizing symptoms had lower SNS and PNS reactivity compared with children with other psychological symptomatology.¹⁰ Interactions between SNS (measured using skin conductance level) and PNS reactivity were a vulnerability factor for externalizing behavior in the context of marital conflict for children aged 7 to 12 years.¹¹

Whether individual vulnerability and contextual risk operates jointly in the onset of physical and psychological symptomatology for children with SCD and other chronic physical health conditions is not firmly established. The limited investigation of the relation between ANS reactivity and chronic physical conditions in childhood has focused primarily on asthma and pain.¹²⁻¹⁴ Emotional responsiveness and ANS reactivity (heart rate, respiration rate) were associated with increased airway reactivity and decreased pulmonary function for children aged 8 to 17 years with asthma.¹³ Children aged 8 to 16 years with recurrent abdominal pain showed greater ANS reactivity (heart rate, systolic, and diastolic blood pressure) to social

stress similar to children with anxiety disorders, when both groups were compared with healthy controls.¹⁴ In a pilot study of ANS reactivity to laboratory stressors, children with SCD aged 5 to 9 years with greater SNS activation (i.e., greater stress reactivity) during challenges compared with rest had more externalizing behavior symptoms and those with greater PNS withdrawal (also indicative of greater stress reactivity) had more SCD clinical complications.¹⁵

This study focuses on middle childhood given the importance of identifying emerging problems early in life to develop interventions to reduce the prevalence of later psychopathology. This study's research questions are directional and based on the prevalence and presumed vulnerability of children with the "classic" ANS reactivity profile-reciprocal SNS activation, and PNS inhibition as demonstrated with healthy children.^{16–18} The research questions are: Do children with SCD and a classic ANS reactivity profile have increased physical and mental health symptoms and child functional impairment compared with children with SCD and other ANS profiles? Do children with SCD and classic ANS reactivity profiles who experience high family stress have increased physical and mental health symptoms and child functional impairment compared with children with SCD and other ANS profiles?

METHODS

This was a cross-sectional design with a convenience sample. The protocol and consent process was approved by the Institutional Review Board of the sponsoring hospital. Inclusion criteria included children 6 to 9 years of age with any diagnosis of sickle cell disease seen at the sickle cell center. Exclusion criteria included health problems preventing full engagement in the protocol.

Measures

MacArthur Health and Behavior Questionnaire¹⁹—The MacArthur Health and Behavior Questionnaire (HBQ 1.0) is a 172-item caregiver-reported measure that assesses children's mental and physical health and functioning. Validity and reliability have been established for diverse clinic-referred and community samples. Items are scored as "yes/no" or 0—"never/not true," 1—"sometimes true," 2—"often/very true." This study used the HBQ sub-scales of child functional impairment, physical health, injuries, and internalizing and externalizing mental health symptoms. Parents rated how much children were impacted by emotional and/or behavioral problems on the functional impairment scale (8 items; Cronbach's $\alpha = 0.62$). The physical health subscale included chronic medical conditions and global physical health (5 items; Cronbach's $\alpha = 0.68$). The injuries subscale consists of 3 items describing the number of injuries in the previous year and interference with activities (Cronbach's $\alpha = 0.92$). Parents reported frequency of children's mental health symptoms in the last 6 months, including depression and anxiety (internalizing—39 items; Cronbach's $\alpha = 0.80$) and conduct problems, inattention, and impulsivity (externalizing—46 items; Cronbach's $\alpha = 0.87$). Cut-points for dichotomizing children as high versus low on internalizing (high >0.54) and externalizing symptoms (high >0.64) have previously been defined,²⁰ with children high on both defined as co-morbid internalizing/externalizing.

Family Stress—Parents completed the Family Inventory of Life Events and Changes,²¹ a 71-item self-report measure of normative and non-normative stressors (e.g., marital, financial, losses, work-family), recorded as having occurred or not in the past year. The Family Inventory of Life Events and Changes has good internal consistency for the total score (subscales are not recommended for use) and good test-retest reliability. In this study, the total score's Cronbach's α was 0.82.

Reactivity Protocol—Children participated in a 20-minute reactivity protocol with demonstrated validity and reliability^{16,22,23} in generating valid measures of autonomic nervous system responsivity for this age group. The protocol was administered at the clinic before potentially stressful medical procedures (e.g., immunizations). The protocol is designed to elicit autonomic responses to challenges across social, cognitive, sensory, and emotion domains. Resting measures were obtained while a researcher read calming stories to the child before and after the other tasks. Next, children completed 4 sets of control tasks paired with challenge tasks similar in physical or social engagement demands, lasting 1 to 2 minutes each. In the social control task, children named items from a picture book; the paired challenge was a structured interview about family, friends, and likes/dislikes. In the cognitive control task, children repeated single digit numbers; the paired challenge involved repeating number sequences. In the sensory control task, children were given drops of water on their tongue; the challenge was drops of concentrated lemon juice. Children watched a neutral movie clip during the emotion control task; the challenge was a movie clip selected to elicit mild fear.

Physiological Measurements—Physiological responses were monitored continuously using the Biopac MP150 System (Biopac Systems www.biopac.com). Respiratory sinus arrhythmia (RSA) and pre-ejection period (PEP) were calculated and averaged for each minute using Mindware (www.mindwaretech.com) software. RSA corresponds to heart rate variability accounting for variations in respiration.²⁴ PEP, derived from Z_0 , dZ/dt , and electrocardiogram waveforms, is the time interval from the beginning of electrical stimulation of the left ventricle to the opening of the aortic valve and reflects the sympathetic nervous system's influence during the cardiac cycle. Autonomic nervous system reactivity measures were summarized as difference scores (challenge task RSA or PEP minus control task RSA or PEP). Overall RSA and PEP reactivity scores were calculated by averaging difference scores for the 4 domains. Given that difference scores are highly correlated with standardized residual scores, difference scores were used because they are easier to interpret. Autonomic nervous system reactivity scores were combined to create domain specific and overall sympathetic nervous system and parasympathetic nervous system reactivity profiles^{11,17,18}—“classic” reactivity (sympathetic nervous system activation and parasympathetic nervous system withdrawal); reciprocal parasympathetic nervous system activation (sympathetic nervous system inhibition and parasympathetic nervous system activation); co-activation (PEP and RSA activation) and co-inhibition (PEP inhibition and RSA withdrawal).

Data Analyses

Data were analyzed using Stata 9.2 and *alpha* was set at 0.05. Pearson and Spearman correlations were conducted to analyze bivariate associations. The main effects of stress and moderating effects of autonomic nervous system reactivity were analyzed for each dependent variable using regression models.²⁵ The number of covariates was limited to maximize power.

RESULTS

Thirty-eight out of 51 (74%) eligible children enrolled in the study and both groups had similar demographic characteristics. Sample descriptive characteristics are shown in Table 1. Consistent with the population affected by sickle cell disease (SCD) in California, 87% of the children were African American/Black race; 8% were Latino, and 5% mixed race. Diagnoses were 63% SCD-SS or SCD-S β^0 and 37% SCD-SC or SCD-S β^+ . Primary caregivers were predominantly mothers (76%); 55% were married or living with a partner; 71% were employed; and 40% reported an annual household income of <\$15,000.

Stress Reactivity

The frequency of the classic autonomic nervous system (ANS) reactivity profile for each domain and for the protocol overall are shown in Table 1. Table 2 shows means, ranges, and standard deviations for the respiratory sinus arrhythmia and pre-ejection period measures at rest; for challenge and task specific controls in each domain; the difference scores for each domain and overall. Respiratory sinus arrhythmia and pre-ejection period difference scores ranged from positive to negative, indicating individual differences from low to high reactivity.

Family Stress, Physical and Mental Health Symptoms, and Physiological Responses

The presence of comorbid mental health symptoms was moderately and positively correlated with the classic ANS profile in the cognitive domain and classic ANS profile overall (Table 1). Family stress was moderately positively correlated with child impairment and classic ANS profile overall. Moderate correlations were found between child sex, age, and parent education with the classic ANS profile (Table 1). Child sex and age were therefore controlled for in subsequent regression models, and parent education was controlled for in models examining associations in the cognitive and emotion domains. The results showed that, for children living in families with high stress, there was an association with high child functional impairment while controlling for ANS reactivity in the sensory domain ($R^2 = 0.38$, $\beta = 0.017 \pm 0.006$, $n = 25$) and overall ($R^2 = 0.51$, $\beta = 0.016 \pm 0.005$, $n = 27$). Results showed there were significant interactions between family stress levels and ANS reactivity in predicting child functional impairment and injuries (Fig. 1). Children with high stress and the classic ANS profile in the cognitive ($R^2 = .58$, $\beta = 0.028 \pm 0.010$, $n = 27$) and emotion ($R^2 = 0.56$, $\beta = 0.037 \pm 0.015$, $n = 25$) domains had the highest levels of child functional impairment. Children with high stress and the classic reactivity profile in the cognitive domain had the most injuries ($R^2 = 0.68$, $\beta = 0.032 \pm 0.011$, $n = 26$).

DISCUSSION

Autonomic nervous system (ANS) reactivity moderated the relation between family stress and child functional impairment with the effects of high family stress most pronounced for children with sickle cell disease (SCD) with the classic ANS reactivity profile. Interestingly, family stress interacted with the classic ANS profile across social, cognitive, and emotion domains to predict both mental and physical health problems. Children with classic ANS profiles who experienced high family stress had increased physical and mental health symptoms and child functional impairment compared with children with the other ANS profiles.

For the reason that previous studies of children's health and ANS reactivity included primarily healthy children, we compared our sample of children with SCD to these studies of healthy children. This study's sample had comparable levels of family stress²¹ and child impairment¹⁹ but a higher prevalence of co-morbid mental health symptoms²⁰ and physical health problems¹⁹ (Table 1). The associations between family stress and child functional impairment²⁶ and ANS reactivity and co-morbid mental health symptoms¹⁰ were also consistent with other research. The prevalence of the classic ANS reactivity profile was similar to that found with physically healthy children of the same age¹⁶; and mean respiratory sinus arrhythmia and pre-ejection period values were similar to those found in other published studies using similar protocols and age groups,^{16,22,23} suggesting that this was a valid protocol for examining ANS profiles for children with SCD.

Our findings suggest that individual differences in the coordinated activity of the parasympathetic nervous system and sympathetic nervous system branches of the ANS can function as risk or resilience factors for mental health outcomes similar to what is seen with physically healthy children.^{11,27} These findings suggest the cumulative effects of SCD and family stress for highly reactive children, consistent with stress-diathesis models that emphasize why some children are more vulnerable to their environments than others.²⁸

Comparing ANS findings across studies and samples is challenging given the lack of standardized assessments. In a study of adults with SCD, parasympathetic nervous system reactivity was shown in response to a hypoxia challenge while healthy controls did not show any ANS changes.²⁹ ANS responses may be unique to specific challenges or stressors.²³ Co-activation was the most prevalent profile for this sample of children with SCD and this may reflect physiological over-arousal or a state of hyper-vigilance that may be adaptive for a time but could also contribute to future dysregulation of the stress response system.

Limitations

Although this study contributed new findings to both pediatric and SCD research, it included several limitations, such as a small sample size, and missing data because of equipment malfunction or human error, which contributed to diminished statistical power. Although we used multiple methods of data collection, we did not include child reports of their health. The study design precludes inferences about the direction of influences of family stress on child outcomes. The lack of a comparison group of community children of similar cultural

and economic background precludes generalization of these results beyond urban children with SCD.

CONCLUSION

Although autonomic nervous system reactivity is an individual difference measure that may be a vulnerability or protective factor depending on the environmental context, future research should examine if patterns of arousal and regulation are similar for children living with other chronic illnesses. The costs to patients and families in diminished quality of life and the burden on the health-care system could be reduced by refining strategies to identify vulnerable children with chronic health conditions. Pediatricians can help identify highly sensitive children with sickle cell disease who experience high family stress because they are vulnerable to experiencing mental and physical health problems and could benefit from stress-reduction interventions.

Acknowledgments

This work was supported by grant 5K23HL76660-4 from the National Heart, Lung and Blood Institute, National Institutes of Health (NIH) (to MJT).

This publication was also made possible by grant UL 1RR024131 from the National Center for Research Resources (NCRR), a component of the NIH and NIH Roadmap for Medical Research.

We thank the study coordinator Ashley Holley; research assistants Juwarat Ains Kadiri, Aaron Toyama, and Gabriel Wong; the staff of the Comprehensive Sickle Cell Center at Children's Hospital & Research Center Oakland; and participating children and families, for their invaluable contributions to the research.

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Figure 1.

Autonomic nervous system (ANS) profiles as moderators in the relation between stress and child impairment and stress and injuries, controlling for child age and sex in all analyses. Parent education also controlled for in cognitive and emotion domain analyses. *Interaction significant at $p < .05$.

Table 1

Characteristics of Sample and Correlations^a Among Demographic, Moderator, Predictor, and Outcome Variables

	1	2	3	4	5	6	7	8	9	10	11	12
Descriptive Statistics % (n) or M (SD)												
Demographics												
Child sex	—											
Child age	.27	—										
Parent education	.02	.12	—									
Graduate degree												
Domain												
Classic ANS reactivity profile ^b												
Social	.14	-.20	-.10	—								
Cognitive	-.39	.13	-.38	-.23	—							
Sensory	-.22	-.31	.01	.01	-.20	—						
Emotion	-.22	-.21	.35	-.27	.15	.07	—					
Overall	.23	.37	.21	-.12	-.09	-.11	-.11	—				
Total family stress	-.00	-.09	.09	.19	-.09	-.17	-.17	.11	—			
Dependent variables												
Child impairment	.06	-.10	.08	.16	-.01	-.18	-.10	.42	.41	—		
Comorbid mental health symptoms	-.08	-.02	-.10	.21	.41	.01	-.27	.40	.23	.36	—	
Physical health problems index	.04	.10	-.04	.07	.02	.20	.05	.00	-.02	.24	.07	—
Injuries	.10	-.07	.40	-.06	.14	.23	.28	-.12	.12	.31	.23	.46*

^a Spearman ρ correlations for nominal and categorical variables; Pearson r correlations for continuous variables.

^b "Classic" reactivity profile in each domain defined as parasympathetic inhibition and sympathetic activation.

^c In a sample of 7- to 8-year-old children (n = 131), 14% displayed the "classic" ANS reactivity profile [16].

^d In a sample of N = 1997 individuals across the lifespan, Family Inventory of Life Events and Changes M = 8.8 (5.9), range 0 to 17 events [21].

^e In samples of 6- to 8-year-old children (sample sizes ranging from n = 469 to n = 601) descriptive statistics included child impairment M (SD) = 0.29 (0.31); physical health problems Index M = 0.49 (0.23); injuries M = 0.51 (0.17) [19].

^f In a sample of N = 328, 7 to 8 year olds, 3% (n = 10) had co-morbid internalizing/externalizing symptoms [20].

* $p < .05$. Because of small sample sizes, other moderate correlations were not statistically significant.

ANS, autonomic nervous system.

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Table 2

Physiological Responding by Domain (N = 37)

Domain	Block		Mean	SD	Range	Difference Scores ^a		
						Mean	SD	Range
RSA								
Rest	Social	1 Resting story 1	6.68	1.42	3.82–9.89			
		2 Picture-naming: social control task	6.89	1.47	4.23–10.38	0.23	0.97	–1.03 to 4.39
Cognitive		3 Social interview challenge	6.93	1.63	4.39–12.02			
		4 Number repeat: cognitive control task	6.09	1.43	3.31–8.81	0.62	0.74	–0.95 to 2.24
		5 Number sequence recall challenge	6.71	1.37	3.81–9.20			
Sensory		6 Water taste sensory control task	7.02	1.44	3.81–9.41	–0.25	1.68	–6.39 to 6.37
		7 Lemon juice taste challenge	6.76	1.48	2.90–9.17			
Emotion		8 Neutral movie: emotion control task	6.80	1.55	3.55–10.49	–0.01	1.36	–7.61 to 1.70
		9 Fear movie challenge	6.98	1.73	3.52–12.19			
Rest		10 Resting story 2	6.58	1.47	3.30–8.91			
		Overall challenge tasks ^b	6.83	1.47	3.84–10.30			
Overall difference scores ^b								
PEP								
Rest	Social	1 Resting story 1	79.43	10.07	51.15–104.08			
		2 Picture-naming: social control task	78.84	10.01	49.20–97.75	0.53	2.58	–6.50 to 7.97
Cognitive		3 Social interview challenge	79.91	9.48	50.85–98.30			
		4 Number repeat: cognitive control task	79.71	10.47	51.95–107.10	0.10	1.64	–4.67 to 4.40
		5 Number sequence recall challenge	79.81	10.06	54.15–105.73			
Sensory		6 Water taste sensory control task	80.38	8.52	54.70–96.10	–0.43	2.16	–7.15 to 2.75
		7 Lemon juice taste challenge	80.88	10.04	53.50–107.10			
Emotion		8 Neutral movie: emotion control task	80.41	10.78	57.35–108.48	–0.35	1.78	–3.75 to 3.57
		9 Fear movie challenge	81.08	11.28	53.60–112.05			
Rest		10 Story 2	80.79	10.81	54.05–108.75			
		Overall challenge tasks ^b	80.28	9.89	53.03–105.52			
Overall difference scores ^b								
						0.03	0.92	–2.31 to 2.80

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^a Challenge minus task specific control.
^b Mean of social, cognitive, sensory, and emotion domains.

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