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Original Articles

Wired for Threat: Clinical Features of Nervous System Dysregulation in 80 Children

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ABSTRACT

BACKGROUND: The negative effect of perceived stress on health has become a cultural epidemic. Despite many health implications, the clinical impact of stress on the nervous system is not well understood. This case series describes the symptom profiles of 80 children with nervous system dysregulation attributed to maladaptive neuroendocrine responses to stress.

METHODS: We reviewed of 80 children with nervous system dysregulation identified from a single, tertiary care pediatric neurology clinic. Included patients were between five and 17 years of age, with unexplained medical symptoms lasting three months or longer affecting at least four of six neurological domains: (1) somatization, (2) executive function, (3) autonomic function, (4) digestion, (5) sleep, and (6) emotional regulation. Medical symptoms, diagnoses, and detailed social histories were collected.

RESULTS: Of 80 children, 57 were female (71%), 57 were Caucasian (71%), with median age of 14 years. Symptoms had a mean duration of 32 months, and included: 100% somatic symptoms, 100% emotional dysregulation, 92.5% disrupted sleep, 82.5% autonomic dysregulation, 75% executive dysfunction, and 66% digestive problems. Overall, 94% reported chronic or traumatic stressors; adverse childhood experiences were present in 65%.

CONCLUSIONS: Perceived stress impacts many functions of the neuroendocrine system through experience-dependent plasticity, resulting in a constellation of symptoms and functional impairments we describe as nervous system dysregulation. The pathophysiology of these symptoms involves dysregulation of subcortical, hormonal, and autonomic circuits, which remain largely untested. Recognition and understanding of maladaptive neurophysiology in stress-related symptoms has important implications for diagnosis, treatment, and advances in health research.

Introduction

Stress has been dubbed the "health epidemic of the 21st century," and the World Health Organization estimated that mental illness, including stress-related conditions, would be the second leading cause of disabilities by the year 2020.[1] While chronic workplace and school

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stress are widely reported in the media, childhood traumatic stress is also becoming increasingly recognized. In a survey of over 8000 adults in the Adverse Childhood Experiences (ACEs) Study, traumatic childhood exposures were common: 12.5% reported domestic violence, 18.8% had a household member with mental illness, 22% had a history of sexual assault, and 25.6% reported substance abuse in the home.[2] Prior studies have demonstrated an association between childhood adversity and medical symptoms such as chronic pain, digestive problems, anxiety, and problems with learning and memory.[3-5] Emerging research in the past three decades has created a new understanding of the complex neurophysiological adaptations to stress, and their relationship to chronic health conditions.[6-8]

Stress triggers autonomic, endocrine, and behavioral responses regulated by multiple brain circuits and neurochemical systems.[6,9] Interpretation of stimuli, as either safe or threatening, is perceived subcortically by the amygdala, with contextual memory influences from the hippocampus, and conscious modulation by the prefrontal cortex. Upon perceived threat, the limbic system triggers autonomic responses in the brainstem via the hypothalamus and central autonomic network, leading to a reduction in parasympathetic vagal activity and increase in sympathetic activity.[10] The decrease in vagal activity creates a rapid increase in heart rate and reduction in digestive, immune, and reproductive function to prepare for the metabolic demands of the "fight-or-flight" response.[9] The sympathetic nervous system triggers a hyper-arousal response, with more sustained heart rate elevation, augmented blood flow to muscles, and increased alertness. The hypothalamic-pituitary-adrenal axis (HPA-axis) coordinates a hormonal response by releasing catecholamines from the adrenal gland. When threat is removed, the vagus nerve recovers its function to execute rest, digest, repair, and restorative functions. In this manner, the nervous system forms a complex, yet critical network to support health and self-preservation in response to brief, intermittent periods of threat[6,9] (Fig 1).

In instances when stress is profound or sustained, the body's stress response may become chronically activated by external or internal threat cues, causing tonic sympathetic hyperarousal.[11,12] The vagus nerve may exhibit reduced parasympathetic activity evidenced by low high-frequency power on heart rate variability testing.[13,14] Cortisol levels are controlled through a negative feedback loop on the HPA-axis; however, when chronically stimulated, this hormonal circuit is also disrupted leading to excessive or depleted cortisol levels.[15] Early life trauma is also associated with upregulation of receptors and epigenetic changes in genes involved in the stress response pathway.[16-18] Through biochemical modifications and experience-dependent plasticity, adaptations to stress can lead to neural, hormonal, and structural alterations within the nervous system.[6-8,19-22]

Stress-related symptoms often co-occur, and commonly involve the somatic, autonomic, and enteric nervous system. Patients are provided with descriptive diagnoses, such as vestibular migraine or irritable bowel syndrome (IBS), which do little to help patients understand how stress may be impacting their body. Nervous system dysregulation is a novel term to describe the clinical symptoms that result from repeated activation or extended conditions of stress on the nervous system. This diagnosis avoids the stigma associated with the term "psychosomatic," and instead provides patients with a useful diagnosis and rationale to explain their medical problems, as well as suggesting pathways for possible therapeutic interventions. In our prior study, nervous system dysregulation had an estimated prevalence of 17% in a tertiary care pediatric neurology clinic, and was associated with ACEs.[23] This case series describes the symptoms of 80 children with nervous system dysregulation, defined as the co-occurrence of at least four medically unexplained symptoms involving a minimum of four of six neurological domains: (1) somatic symptoms, (2) executive function, (3) autonomic regulation, (4) digestive function, (5) emotional regulation and (6) sleep. We aimed to describe the clinical features and reported stressors of these patients, and to provide a rationale for the term "nervous system dysregulation" according to the physiological impact of chronic stress on the nervous system.

Materials and Methods

Included patients were seen at a general pediatric neurology clinic at Stanford Children's Health, a tertiary care center, from June 2015 until December 2017. A board-certified pediatric neurologist (J.E.) assessed all patients, including a standardized set of questions to evaluate six neurological domains: somatic symptoms, executive function, autonomic symptoms, digestive problems, emotional regulation, and sleep. Children ages five to 18 years old, with at least four affected neurological domains, for a duration of at least three months, were included. Children with moderate-to-severe intellectual disability or developmental delay were excluded. Laboratory testing (complete blood count, metabolic panel, iron studies, thyroid function, erythrocyte sedimentation rate, and antinuclear antibody), magnetic resonance imaging of the brain and spine, electroencephalogram, electrocardiogram, and autonomic testing (using tilt table) were performed as clinically indicated. Patients with an abnormal neurological examination, autoimmune disease, thyroid disease, or other medical diagnosis that may account for their symptoms were excluded. Electronic patient medical records were reviewed to collect demographics, clinical presentation according to parent and child report, physical examination and other reported medical diagnoses. Seventeen patients have been previously described.[23]

The six neurological domains were defined as follows. *Somatic symptoms* included chronic pain (migraine, tension-type headache, chronic daily headache, abdominal pain, or other body pain), chronic photophobia, and functional neurological deficits (hyperkinetic movements, weakness, paraesthesias, vision complaints, or nonepileptic events). *Executive dysfunction* consisted of poor memory or attention problems resulting in impaired school performance according to patient and/or parent report. *Sleep disturbances* included insomnia (sleep latency longer than 30 minutes), frequent night waking (twice or more per night), or subjective report of frequent nightmares. *Autonomic dysregulation* included symptoms of hyperhidrosis, intermittent or chronic orthostatic dizziness, or recurrent (≥ 2) episodes of vasovagal syncope. *Digestive problems* involved dysfunction of the enteric nervous system including gastro-esophageal reflux, nausea, diarrhea, constipation, and dyspepsia. *Emotional dysregulation* included personal reports of emotional lability, panic attacks, suicidality, and co-morbid diagnoses of depression or anxiety by a psychiatrist or psychologist.

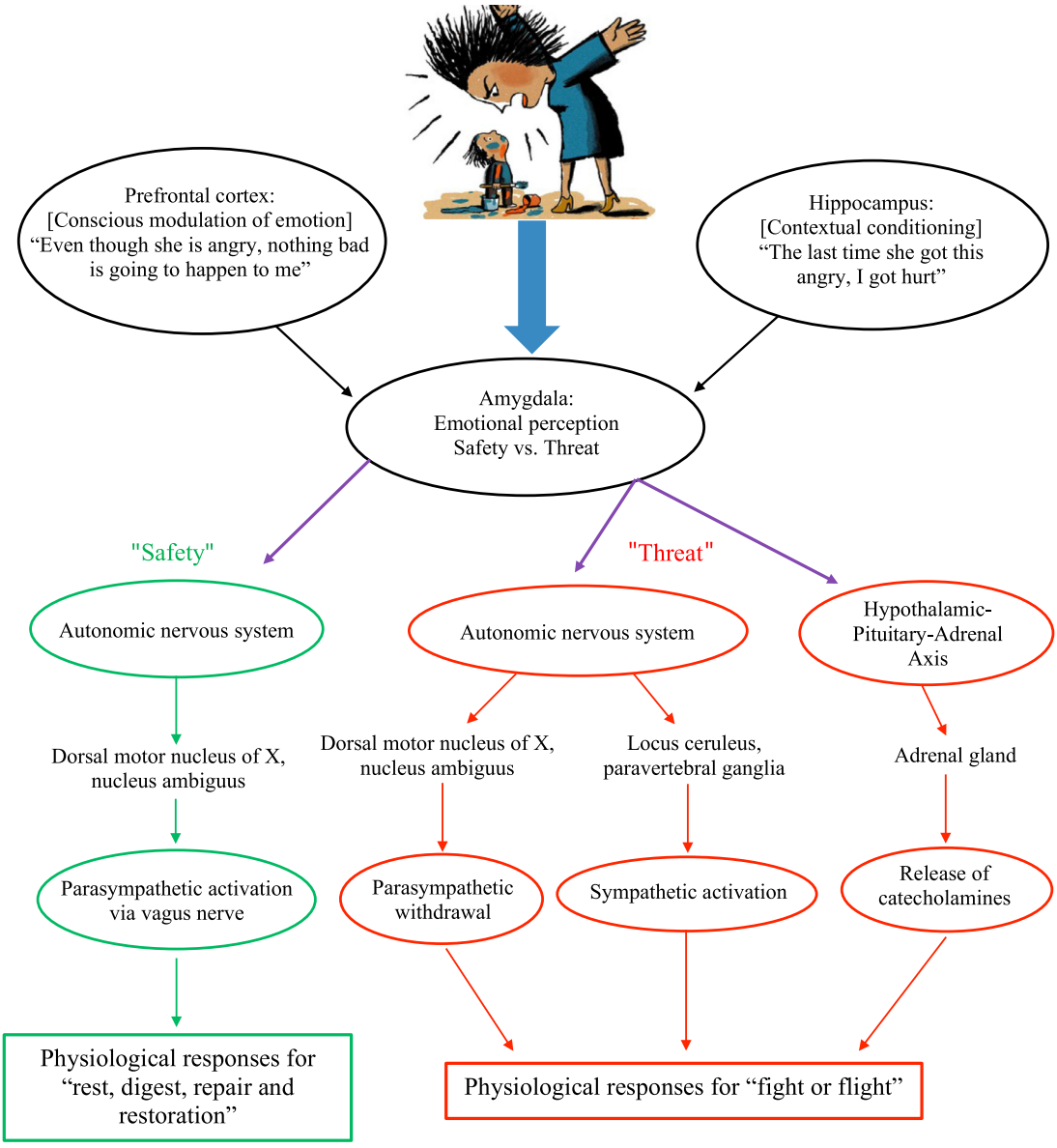

FIGURE 1. Physiological response to safety or threat: The amygdala is involved in interpreting external stimuli as "safe" or "threatening" and processing these emotional responses. The prefrontal cortex exerts a moderating influence over the amygdala, while the hippocampus generates contextual information from the memory of past experiences. When safety is perceived, the vagal nuclei in the brainstem are activated via the central autonomic network (purple), and the parasympathetic nervous system directs physiological responses for rest, digest, repair and restoration (green pathway). If threat is detected, the central autonomic network (purple) coordinates the stress response, with vagal withdrawal and sympathetic activation through the brainstem and hypothalamic-pituitary-adrenal axis. This generates the physiological responses for "fight or flight" (red pathway). "The color version of this figure is available in the online edition."

The pediatric neurologist (J.E.) collected a standardized social history in all patients. Care was taken to create a trusting therapeutic relationship among the child, parent, and provider. There is currently no validated tool for collecting ACEs in children; however, the Center for Youth Wellness is currently developing such a tool for health professionals. In accordance with the original ACE study[2] social histories included a series of questions regarding household members, exposure to domestic violence, substance abuse in the home, parental and peer relationships, family history of psychiatric illness, and history of trauma or abuse. Information obtained from subsequent visits was included in data collection. Children 12 years of age or older were interviewed in private, and parental corroboration was not required. Disclosure of events that jeopardized a child's safety were reported to local Child Protective Services. ACEs were recorded under nine categories as reported in prior studies[2,4]: (1) physical abuse, (2) emotional abuse, (3) sexual abuse, (4) emotional or physical neglect, (5) incarcerated household member, (6) exposure to domestic violence, (7) substance user in the home, (8) mental illness in a household member, and (9) being raised by one parent or by adults other than parents. The sum of ACEs in each patient were reported as the total ACE score. Additional experiences reported as stressful by patients or families were also recorded and were labeled as negative life events, but were not included in the total ACE score. Overwhelming school pressure was

TABLE 1. Demographic Characteristics of Children with Nervous System Dysregulation

Characteristic		n (N = 80)	Percent
Demographics			
	Female	57	71.2%
	Median age (range)	14.3 years (5-18 years)	
Racial Identity			
	Caucasian	57	71.2%
	Hispanic	13	16.2%
	Asian	3	3.7%
	Other	7	8.8%
Medical Insurance			
	State-funded (Medi-Cal)	34	42.5%
	Blue Cross/Blue Shield	23	28.8%
	Aetna/Cigna	11	13.8%
	Veterans Association	1	1.2%
	Other	11	13.8%

also recorded. Institutional ethics board approval was obtained for this study.

Results

Eighty children were included; 57 were female (71.2%), with median age 14 years. The majority of patients were Caucasian (71.2%), and on state-funded medical insurance (42.5%) (Table 1). The duration of symptoms from onset to the time of initial assessment ranged from three months to 10 years, with a median of 32 months. The following functional impairments were reported: 100% somatic symptoms, 100% emotional dysregulation, 92.5% disrupted sleep, 82.5% autonomic dysregulation, 75% executive dysfunction, and 66% digestive problems (Table 2). Nervous system dysregulation involved all six neurological domains in 37.5% of patients, five domains in 41%, and four domains in 21%.

Somatic: All 80 patients reported somatic symptoms (Table 2): 78 (97.5%) with chronic pain, most commonly chronic daily headache (46%), migraine (35%), and abdominal pain (33.8%) (Fig 2). Functional neurological deficits were present in nearly half of patients (47.5%). Six patients were diagnosed with nonepileptic events (7.5%), characterized by rhythmic movements, unresponsiveness, and normal ictal electroencephalography.

Emotional self-regulation

All 80 patients reported difficulties with emotional self-regulation (Table 2), including clinically significant anxiety (90%) or emotional lability (67.5%). Two-thirds of patients had a history of panic attacks (62.5%). Over half of patients had a clinical diagnosis of depression (53.8%), and one-quarter disclosed current or past history of suicidality (26.3%) or self-harm behaviors (23.8%). Over one-third (36%) were taking antidepressant medication (Table 3).

Sleep

Sleep difficulties were reported in 92.5% of patients (Table 2); including insomnia (69%) and frequent night waking (37%). One-third of patients were taking melatonin on a regular basis (37.5%), and 10% were being treated with trazodone (Table 3).

TABLE 2. Clinical Features of Children with Nervous System Dysregulation

Clinical Presentation		n (N = 80)	Percent of Total
Somatic symptoms		**80**	**100%**
	Chronic pain	78	97.5%
	Chronic photophobia	27	33.8%
	Hyperkinetic movements	17	21.3%
	Paresthesias	14	17.5%
	Vision problems	14	17.5%
	Weakness (focal or global)	8	10%
	Nonepileptic events	6	7.5%
	Abnormal gait	1	1.3%
Emotional self-regulation		**80**	**100%**
	Anxiety	72	90%
	Emotional lability	54	67.5%
	History of panic attacks	50	62.5%
	Depression	43	53.8%
	Suicidality	21	26.3%
	Self-harm behaviors	19	23.8%
	Substance use disclosed	10	12.5%
Sleep disruption		**74**	**92.5%**
	Insomnia	69	86.3%
	Frequent night waking	37	46.3%
	Nightmares	18	22.5%
Autonomic dysregulation		**66**	**82.5%**
	Orthostatic dizziness	55	68.8%
	Recurrent vasovagal syncope	13	16.3%
	Hyperhidrosis	13	16.3%
Executive dysfunction		**60**	**75%**
	Attention problems	51	63.8%
	Memory problems	32	40%
	School accommodations	47	58.8%
Digestive problems		**53**	**66.2%**
	Chronic nausea	32	40%
	Constipation	30	37.5%
	Gastroesophageal reflux	16	20%
	Diarrhea	8	10%
	Oral aversion	3	3.8%
	Dysphagia	2	2.5%
Chronic fatigue		**52**	**65%**

Autonomic regulation

Symptoms of autonomic dysregulation were present in 82.5% of patients (Table 2). Eight patients (10%) fulfilled clinical criteria for postural orthostatic tachycardia syndrome (POTS), with elevation of 40 beats per minute above baseline heart rate within five minutes of standing. Autonomic testing with tilt table was performed in six patients, all of whom demonstrated abnormalities. Autonomic abnormalities involved primarily sympathetic vasomotor, sudomotor, and cardiovascular fibers in all patients, with relative sparing of the parasympathetic and baroreflex cardiovascular pathways. Only one patient with nocturnal sweating, recurrent syncope, POTS, chronic fatigue, and nonepileptic events demonstrated additional parasympathetic involvement of the

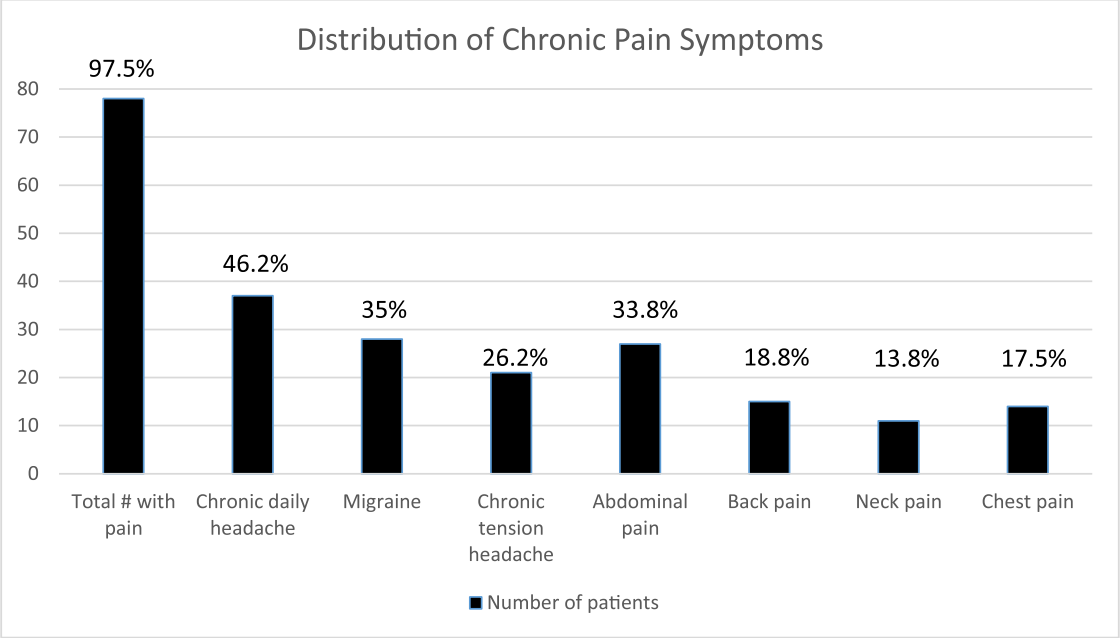

FIGURE 2. Distribution of chronic pain symptoms in children with nervous system dysregulation ($N = 78$).

cardiovascular fibers. The remainder of autonomic symptoms are reported in Table 2.

Executive function

Difficulties with executive function were reported in 75% of patients (Table 2), including problems with attention (63.8%), and short-term memory (40%). Attention deficit hyperactivity disorder was diagnosed in 38.8%. Over half of patients (58.8%) required school accommodations, including individual education plans, 504 plans, or home-schooling.

Digestion

Digestive problems were reported in 66% of patients (Table 2), including chronic nausea (40%), constipation (37.5%), gastroesophageal reflux (20%), and diarrhea (10%). Eight patients had a diagnosis of IBS, and five patients had been diagnosed with ulcers or gastritis (Table 3).

Stressful life events

The majority of patients (94%) reported stressful life events (Table 4). At least one ACE was reported by 65% of patients, with a median ACE score of 1, mean ACE score of 1.7, and range of 0 to 6. One-third of patients reported a history of emotional or verbal abuse by a parent, one-third had a household member with mental illness, and one in six patients were exposed to domestic violence or substance abuse in the home. In addition, 43.8% of patients reported other negative life events or chronic stressors. Forty percent reported overwhelming school pressure. Ten patients (12.5%) reported a high performing "perfectionist" attitude, and overwhelming school pressure as the only main stressors. Only five patients (6%) did not disclose a significant life stressor.

Discussion

In this large case series, we detail the clinical features of 80 pediatric patients who experience symptoms across multiple neurological domains, and the presence of antecedent or concurrent stressors. Prior literature has described how the developing nervous system is particularly susceptible to the effects of toxic or chronic stress through experience-dependent plasticity,[22,24] and how this may have long-term effects on mental and physical health.[7,8,19,20] In this study, stressful life experiences were disclosed by 94% of patients. In a prior study, ACEs were associated with this clinical profile.[23] While ACEs accounted for stressors in 65% of patients in this larger series, 44% of patients disclosed additional stressors not included in the ACE questionnaire, such as overwhelming school pressure, bullying, or perceived life-threatening illness/event of self or a loved one. Ten patients (12.5%) did not disclose any specific negative life events, but were self-reported "perfectionists" or over-achievers, who reported a high degree of self-imposed stress for performance in school and extra-curricular activities. This observation suggests that the perception of stress is highly individualized, and that ACEs are not the only stressor that can impact a child's health. Cortical and subcortical circuits help to contextualize an experience and modulate the stress response in accordance with associated memories and the perception of control. In children, developmental immaturity of the prefrontal cortex limits the capacity for conscious modulation of the stress response. The wide breadth of stressors identified

TABLE 3. Additional Medical Problems and Medications in Children with Nervous System Dysregulation

Medical Diagnoses		n (N = 80)	Percent
Somatic symptoms			
	Chronic daily headache	37	46.3%
	Migraine	28	35%
	Nonepileptic events	6	7.5%
Psychiatric			
	Obsessive compulsive disorder	10	12.5%
	Post-traumatic stress disorder	7	8.8%
	Eating disorder	4	5%
Sleep			
	Obstructive sleep apnea	13	16.3%
Executive function			
	Attention Deficit Disorder	31	38.8%
Autonomic			
	Postural Orthostatic Tachycardia syndrome	8	10%
Digestive			
	Gastroesophageal reflux	16	20%
	Irritable bowel syndrome	8	10%
	Peptic ulcer disease (ulcers, gastritis)	5	6.3%
Other			
	Overweight (BMI ≥ 85%ile for age)	40	50%
	Obesity (BMI ≥ 95%ile for age)	28	35%
	Asthma	31	38.8%
	Heart palpitations	20	25%
	Abnormal menses (N = 45 females ≥13 years old)	9	20%
	Idiopathic juvenile scoliosis	11	13.8%
	Nonspecific T2 hyperintensities on brain MRI	8	10%
Medications			
	Melatonin	30	37.5%
	Antidepressants	29	36.3%
	Anticonvulsants	15	18.8%
	Antihistamines	14	17.5
	Antipsychotics	10	12.5%
	Antihypertensives	10	12.5%
	Trazodone	8	10%
	Benzodiazepines	4	5%
	Opioids	2	2.5%

Abbreviations:
BMI = body mass index
MRI = magnetic resonance imaging.

TABLE 4. Profile of Stressful Life Events in Children with Nervous System Dysregulation

Stressful Life Event	n (N = 80)	Percent
Adverse Childhood Experiences	52	65%
Physical abuse	10	12.5%
Emotional/verbal abuse	22	27.5%
Sexual abuse or assault	10	12.5%
Physical or emotional neglect	4	5%
Incarcerated household member	4	5%
Exposure to domestic violence	13	16.3%
Substance user in the home	14	17.5%
Household member with mental illness	25	31.3%
Single parent/parental death or abandonment	31	38.8%
Median ACE score (range)	1 (0-6)	
Mean ACE score	1.7	
Negative Life Events	35	43.8%
Bullying by peers	15	18.8%
Personal life threatening illness or event	8	10%
Adopted/foster care	7	8.8%
Homeless	6	7.5%
Death of a loved one	6	7.5%
Family member with life threatening illness or event	3	3.8%
Personal identity/sexual orientation	3	3.8%
Overwhelming school pressure	32	40%
High performer/"perfectionist" + school pressure	10	12.5%
No stressor disclosed	5	6%

in this study supports the premise that any experience subjectively perceived by the child as stressful can activate the stress response, and if prolonged, may lead to dysregulation of associated neural and hormonal systems. While it is important to screen patients for ACEs, identification of a readily defined stressor is not necessary for the clinical diagnosis of nervous system dysregulation.

Emerging evidence over the last three decades has identified neurophysiological correlates to chronic and toxic stress, indicating dysregulation and neuroplasticity of central nervous system networks, the autonomic nervous system and HPA-axis.[6-9,19-21,25] Prior literature has also established a correlation between these physiological aberrations and the clinical symptoms described herein.[7,26-34] Based on this literature and the clinical profiles observed in this study, we provide a more useful, clinically relevant term "nervous system dysregulation," and propose the acronym "S-T-R-E-S-S" to organize the neurological domains associated with stress: (1) somatic symptoms, (2) thinking, (3) autonomic regulation, (4) enteric function, (5) self-regulation, and (6) sleep.

Somatic symptoms

A majority of patients with nervous system dysregulation experience chronic pain. Prior studies have established an association between ACEs and pain conditions,[5] with implications for maladaptive stress responses.[29,35] The transition from acute to chronic pain has also been associated with a maladaptive stress response, dysfunctional cortisol responses and structural changes in gray matter volume and connectivity of the prefrontal cortex, amygdala, and hippocampus.[5,28,35,36]

Functional neurological deficits, such as hyperkinetic movements or nonepileptic events, exhibit features of autonomic dysregulation. Sympathetic hyperarousal has been observed in patients with essential tremor,[37] and tics,[38] and pharmacologic treatments that reduce sympathetic tone are often helpful in these patients. Autonomic abnormalities have also been observed in patients with nonepileptic events. In a study of 20 adults with nonepileptic events, or pseudoseizures, continuous heart rate variability monitoring demonstrated ictal and peri-ictal autonomic changes characterized by a preictal increase in sympathetic activity, and an increase in parasympathetic activity during and after the event.[39] This study finding suggests that the pathophysiology of pseudoseizures may include neural dysregulation of the autonomic nervous system which is traditionally untested. Further research is necessary to confirm these preliminary findings.

Executive function (Thinking)

In this series, 75% of children reported problems with attention or memory, and school accommodations in 59%.

Almost 40% had a diagnosis of Attention Deficit Hyperactivity Disorder. The high rate of executive dysfunction reported in this case series is consistent with the learning and cognitive processing difficulties reported in children with ACEs[4] and patients with post-traumatic stress disorder (PTSD),[40] and suggests alterations in functional networks of the prefrontal cortex that may be related to chronic stress. While acute stress can promote arousal, vigilance and enhanced memory, excessive catecholamines, and glucocorticoids associated with prolonged stress lead to neuronal loss, particularly in the hippocampus, with impaired learning and memory.[30] Structural neuroimaging studies in children have shown that exposure to maltreatment or sustained stress is associated with reduced gray matter volumes in the prefrontal cortex, cingulate gyrus, insula, and hippocampus.[41-43] Other studies have further correlated structural changes in the prefrontal cortex with impairments in cognitive performance, working memory, and attention.[30,41,44] Difficulties in attention and school performance are often attributed to somatic complaints; however, further research is necessary to determine if this relationship is causative or correlative.

Autonomic regulation

The autonomic nervous system is a critical mediator of the acute stress response and recovery.[9] Studies of autonomic function using heart rate variability in adults and children with depression, PTSD or a history of ACEs demonstrate dysregulated autonomic control, typically with increased sympathetic and decreased parasympathetic activity.[12,14,45,46] Recent studies have linked early childhood adversity with differences in stress-induced autonomic reactivity,[9,47] which may offer an evolutionary advantage through a hypersensitive stress response. While different patterns of physiologic reactivity can offer a resilience advantage, such adaptations may also lead to clinical consequences. Numerous stress-related symptoms have been associated with dysregulated autonomic control including migraine,[26,27] orthostatic dizziness,[48] and syncope.[49] Autonomic dysregulation is also frequently observed in patients with chronic fatigue syndrome[31] and POTS.[50] In this series, nearly two-thirds of patients reported symptoms of chronic fatigue (65%), and 10% fulfilled criteria for POTS. The clinical profile of nervous system dysregulation does not exclude patients with POTS or chronic fatigue syndrome, and may help to explain why many of these patients have co-morbid symptoms of chronic pain, cognitive complaints, sleep problems, and digestive symptoms, which are seemingly unrelated to orthostasis or fatigue.[51] Further research is necessary to characterize the autonomic and hormonal disturbances across these groups of patients, and their relationship to perceived chronic or toxic stress.

Enteric dysfunction

In this series, 66% of patients had digestive complaints involving the enteric nervous system. The gut-brain axis consists of bidirectional neural and hormonal communication between the brain and the digestive system for gut homeostasis, and also links emotional and cognitive centers of the brain with intestinal function.[52] Stress and emotional states affect various aspects of enteric function, including delayed gastrointestinal motility, increased visceral sensitivity, increased intestinal permeability, and modulation of the human gut microbiota.[53] Alterations in autonomic function and HPA-axis activity have been identified in patients with gastro-esophageal reflux, IBS, peptic ulcer disease and inflammatory bowel disease.[34,54,55] In one study, diarrhea-predominant IBS was differentiated from constipation-predominant IBS and control subjects, with increased postprandial sympathetic dominance secondary to vagal withdrawal and a two-fold increase in cortisol that correlated with postprandial symptoms.[55] Peptic ulcer disease is perhaps the closest biopsychosocial model of disease, with the presence of *Helicobacter pylori*, lifestyle habits, and psychological stress acting as co-mediators of disease. In a recent study, however, psychological stress was associated with gastric and duodenal ulcers, irrespective of *Helicobacter pylori* and lifestyle habits.[56] Further research is necessary to assist in identifying the neural, hormonal, and gut microbiota changes due to stress, and their potential contributions to diseases of the enteric nervous system.

Emotional self-regulation

Anxiety disorders and depression are becoming increasingly prevalent in the general population and are associated with an increased risk of substance abuse, co-morbid health problems, and suicidality. Given the associated societal and economic implications, early recognition and treatment of these disorders in childhood is imperative. In this case series, all 80 patients demonstrated difficulties with emotional regulation: 90% reported clinically significant anxiety and two-thirds (62.5%) experienced panic attacks. Over half of patients (54%) had a co-morbid diagnosis of depression. Recent evidence suggests that early life experiences of fear or trauma may sensitize developing cortico-limbic pathways and the HPA-axis to react more readily to threatening stimuli by upregulating neurobiologic stress responses.[32] A hyper-sensitive amygdala may be observed clinically as hypervigilance and anxiety, which may further perpetuate the cycle of nervous system dysregulation. The impaired ability to recover from an emotional challenge can result in panic attacks and depression. According to results from the ACE study, exposure to at least one ACE accounted for 54% of the population attributable risk for depression, and 67% for suicide attempts.[57] In our study, 26% of patients with nervous system dysregulation had a history of suicidality. Suicidality is becoming an increasing concern for teenagers across demographics and socioeconomic status, and further study is necessary to determine if patients with a clinical profile of nervous system dysregulation are at increased risk for suicide attempts.

Sleep

In this series of pediatric patients, 92.5% reported sleep problems. From an evolutionary perspective, chronic threat promotes a physiological state of arousal, and interferes with the onset and maintenance of deep sleep in order to promote survival. Scientifically, however, the causal relationship between stress and sleep disorders has been difficult to prove due to reciprocal

interactions between sleep and dysregulations within the HPA-axis[58] and the autonomic nervous system.[33] Stress is a frequent precipitating factor for sleep problems, with objective sleep changes occurring even in the setting of minor daily stress.[58] In a systematic review, a history of ACEs was associated with multiple sleep disorders in adults, including insomnia, nightmares, and sleep apnea.[59] In our patient population, 13 children (16%) had obstructive sleep apnea, of whom only five had co-morbid obesity. Stress affects sleep through changes in autonomic function, with a decrease in parasympathetic modulation and increased sympathovagal balance,[60] as well as dysregulated cortisol patterns.[58] While insomnia and sleep apnea have been associated with HPA-axis and autonomic dysregulation,[33,58,61] it has been difficult to discern if these are causal or secondary to these physiological changes. While this study does not help to elucidate the causal relationship among stress, sleep disorders, and nervous system dysregulation, it does support their strong association, and highlights the need for further research in this area.

Limitations

Limitations of the current study are as follows. First, although there is adequate research to support the pathophysiological premise of nervous system dysregulation, autonomic and neuroendocrine function is not routinely available, and was not tested in these patients. In addition, formal cognitive testing and sleep analysis would confirm subjective symptom reporting. This study was conducted as a preliminary study to illustrate the constellation of symptoms and medical problems in this patient population, and to demonstrate the need for further controlled studies and funding in the area of stress research. Second, there is no current validated tool to assess for the presence of stressors. The ACE questionnaire has not yet been validated in children, and as illustrated in this study, does not include potentially important stressors such as school pressure, bullying, or perceived life-threatening event or illness, which may impact the health and wellbeing of a child. In demonstrating the importance of childhood stress on health, it is our hope that validated tools to assess for important stressors become readily available for pediatricians in the future.

Future directions

The commonly utilized paradigm in clinical medicine that stress-related symptoms are psychological in origin, without an "organic basis," has interfered with the physician's ability to properly diagnose, dialogue with, and adequately treat this group of patients. Neurological investigations limited to cortical electrical function, structural neuroimaging, and peripheral nerve and muscle testing do not adequately assess the areas implicated in stress-related symptoms, which involve subcortical, hormonal, and autonomic circuits. Further research is necessary to test autonomic and neuroendocrine responses to stress and recovery in patients with nervous system dysregulation. By understanding the neurophysiological impact of stress on the nervous system, innovative therapeutic approaches may emerge. Preliminary studies have demonstrated safety and efficacy of novel treatments for post-traumatic stress disorder including mindfulness-based stress reduction,[62] yoga,[63] and physical exercise.[64] Slow rhythmic breathing, an important element of yoga and mindfulness, raises vagal activity and induces a GABA-mediated calming effect on the amygdala.[65] Breathing exercises may be easily taught to pediatric patients in an outpatient clinic setting.

Conclusions

Prior literature has demonstrated that extreme or chronic stress leads to changes in the neuroendocrine system. While these alterations are likely to be adaptive in nature, affording a greater sensitivity and response to future threat, structural and functional changes in the nervous system may also cause neurological symptoms that, in the absence of appropriate testing, remain "unexplained." Nervous system dysregulation is a novel, clinically-defined syndrome that describes the global impact of chronic or toxic stress on the integrated functions of the nervous system: executive function, sleep, emotional regulation, somatic function, digestion, and autonomic function. A history of trauma or ACEs may not be immediately evident to the treating provider unless a careful history is taken, but may significantly impact child development and subsequent health outcomes. Recognizing the impact of perceived stress on children and the developing nervous system has implications for diagnosis, management and future research in health promotion and disease prevention.

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