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Pediatrics 2006;118;309-321
DOI: 10.1542/peds.2005-3032

STATE-OF-THE-ART REVIEW ARTICLE

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Pediatric Autonomic Disorders

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

The scope of pediatric autonomic disorders is not well recognized. The goal of this review is to increase awareness of the expanding spectrum of pediatric autonomic disorders by providing an overview of the autonomic nervous system, including the roles of its various components and its pervasive influence, as well as its intimate relationship with sensory function. To illustrate further the breadth and complexities of autonomic dysfunction, some pediatric disorders are described, concentrating on those that present at birth or appear in early childhood.

www.pediatrics.org/cgi/doi/10.1542/peds.2005-3032

doi:10.1542/peds.2005-3032

Key Words
autonomic nervous system, cardiovascular, sympathetic nervous system, parasympathetic nervous system, viscerosensory

Abbreviations
FD—familial dysautonomia
ANS—autonomic nervous system
CAN—central autonomic network
PHOX2B—paired-like homeobox 2B
NGF—nerve growth factor
CFS—chronic fatigue syndrome
HSAN—hereditary sensory and autonomic neuropathy
CIPA—congenital insensitivity to pain with anhidrosis
CCHS—congenital central hypoventilation syndrome
CVS—cyclic vomiting syndrome
POTS—postural orthostatic tachycardia

Accepted for publication Feb 13, 2006

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APPRECIATION OF THE breadth of autonomic disorders has increased since Langley[1] originally proposed the generic term "autonomic nervous system" (ANS) and designated its division into the sympathetic, parasympathetic, and enteric nervous systems. Although a number of texts dedicated to various aspects of autonomic function now are available,[2–4] they tend to concentrate on adult disorders, with pediatric autonomic disorders poorly represented. Even within the first text dedicated to describing various clinical disorders by Dancis,[5] the only pediatric disorder included was familial dysautonomia (FD). Now, more than 20 years later, investigators are beginning to appreciate the value of genetic autonomic disorders as models to advance the understanding of pathophysiologic mechanisms involved in autonomic dysfunction.[6,7] In fact, the original description of FD in 1949[8] preceded the description by Shy and Drager[9] of the adult neurodegenerative syndrome characterized by central autonomic dysfunction by 11 years. Although the report by Shy and Drager initiated expansion of autonomic research and eventual founding of an autonomic subsection within neurology and autonomic societies in the United States and Europe, the same level of interest has not been seen within the pediatric community. Perhaps this disparity has evolved through lack of awareness of the myriad of pediatric autonomic disorders or inadequate residency education regarding evaluation of this particular system.

The ANS is pervasive and integrates multiple secondary functions so that symptoms can be widespread and confounding. In addition, there are often associated sensory perturbations, because the development and maintenance of the autonomic and sensory systems are closely linked. The goal of this article is to increase awareness of the expanding spectrum of pediatric autonomic disorders so that this population can benefit from the advances being made in evaluation and treatment.[2,3] We provide an overview of the ANS and stress the extent of its influence, discuss the protean symptoms and manifestations caused by autonomic perturbations, and emphasize the expanding number of pediatric disorders that feature autonomic dysfunction.

THE ANATOMY AND PHYSIOLOGY OF THE ANS

General Description

The ANS is a visceral and largely involuntary motor/effector system that is traditionally divided into sympathetic (thoracolumbar) and parasympathetic (craniosacral) divisions, each with a central and a peripheral component.[10] In addition, there is an important enteric division. Outflow can occur independently, but to some extent it is regulated and integrated by the central autonomic network (CAN).[11] The CAN maintains integral relationships with visceral sensory neurons via afferent input from the vagus nerve and relays transmission through the nucleus tractus solitarius to the hypothalamus, amygdala, and forebrain.[11]

Embryologic Development

Development of the ANS is intimately related to the development of the sensory nervous system; both have their embryonic origins in the multipotential neural crest cells. These cells migrate and eventually evolve into sensory and autonomic ganglia as well as the adrenal chromaffin cells. Their differentiation and commitment to function in the mature nervous system is incumbent on exposure to growth factors released by structures along the migratory route and then within the target tissue. Eventually, specificity will be determined by their ability to produce specific neurotransmitters. Therefore, one could postulate that an early genetic error affecting initial migration would cause profound decreases in both sensory and autonomic populations, whereas a later genetic error might only affect cell survival to one or both populations, causing more erratic and varied clinical expression.

Growth Factors and Neurotransmitters

Various factors promote normal progression from the embryonic to the mature autonomic and sensory nervous systems.[12,13] Several key transcription factors have been identified that play critical roles in the development of the ANS, such as the *MASH1* (mammalian achaete-scute homologue) and *PHOX* (paired-like homeobox) 2B genes, which are necessary for differentiation of uncommitted neural crest cells to the developing ANS.[14,15] Another important regulator of development and survival is nerve growth factor (NGF).[16,17] In the embryonic neuron, NGF binding promotes migration from the neural crest and enhances maturation through neurite outgrowth. In the mature neuron, dependence on NGF decreases, but it continues to enhance neurotransmitter synthesis.[17]

The peripheral ANS provides physiologic responses that are critical for homeostasis and acute adaptations to stressful circumstances via multiple transmitters and a chemical coding system of autonomic neurons. During the last 2 decades it has become clear that within a single neuron multiple transmitter systems coexist and that within a given ganglion the variety and pattern of neurotransmitters is extensive. In turn, multiple organ systems then respond to the neurotransmitters released via various receptor systems. For both the sympathetic and parasympathetic systems, the preganglionic innervation is largely cholinergic, with terminals releasing acetylcholine at the ganglion synapses. For the sympathetic system, norepinephrine is the major neurotransmitter, but other postganglionic neurotransmitters are also important, among which are substance P, dopamine, and vasoactive intestinal polypeptide. Although the traditional concept is that the sympathetic and parasympathetic

systems are antagonistic, that is not always the case (as indicated in Table 1). Thus, when the sympathetic system is stimulated, a host of receptor systems are activated, including dilation of the pupil, increase in glandular secretions, bronchodilation, increase in heart rate and force of contraction, decrease in gastrointestinal tract motility, decrease in function of the reproductive organs, and mobilization of energy substrates. The parasympathetic system tends to have more focal responses, but some effects may be quite broad, particularly with the wide-ranging innervation of the vagus nerve. However, the parasympathetic system seems to have less influence on exocrine and endocrine function.

INTEGRATION OF THE PERIPHERAL AND CENTRAL AUTONOMIC NERVOUS SYSTEMS

The varied functions of the peripheral ANS are integrated and regulated by the CAN, the extensive circuitry of which ranges from the forebrain to the brainstem (Table 2).[11] Disorders in the forebrain circuits, such as ischemia secondary to blood-flow disturbance or seizures, can cause cardiac arrhythmia.[18] Within this circuitry, the nucleus tractus solitarius in the medulla oblongata, which receives input from the vagus and glossopharyngeal nerves, functions as a major relay station, allowing continuous feedback and integration. The hypothalamic area seems to have major influences on thermoregulation and sleep/wake cycling. Thus, the CAN serves many critical functions and affects visceromotor and neuroendocrine function as well as motor and pain modulation. It aids in reflex adjustments of autonomic responses and integrates autonomic, neuroendocrine, and behavioral responses that, in turn, maintain homeostasis, emotional expression, and response to stress.[19]

TABLE 1 **ANS Functions**

Organ	Sympathetic Nervous System	Parasympathetic Nervous System
Eye		
Pupil	Dilatation	Constriction
Ciliary muscle	Relax (far vision)	Constrict (near vision)
Lacrimal gland	Slight secretion	Secretion
Salivary glands	Slight secretion	Secretion
Heart	Increased rate	Decreased rate
	Positive inotropism	Negative inotropism
Lungs	Bronchodilation	Bronchodilation
Gastrointestinal	Decreased motility	Increased motility
Kidney	Decreased output	None
Bladder	Relax detrusor	Contract detrusor
	Contract sphincter	Relax sphincter
Penis	Ejaculation	Erection
Sweat glands	Secretion	Palmar sweating
Blood vessels		
Arterioles	Constriction	None
Muscles		
Arterioles	Constriction or dilatation	None
Metabolism	Glycogenolysis	None

SYMPTOMS OF AUTONOMIC DYSFUNCTION IN THE PEDIATRIC PATIENT

Because the ANS and its CAN component have pervasive effects that affect multiple other systems secondarily, clinical manifestations can be extremely varied. Rather than use an anatomic approach, one can use a functional or system approach, as listed in Table 3. For this review, only those autonomic disorders with multisystem involvement are considered. Although children with gastroesophageal reflux or asthma have obvious autonomic dysfunction, their care is best relegated to the appropriate subspecialist. However, when more than one system is perturbed, then one might consider that the patient is affected with a more global autonomic disorder. At that point, the differential diagnosis expands and starts to include a number of autonomic disorders that can be considered on the basis of age at presentation.

PEDIATRIC AUTONOMIC DISORDERS

Many pediatric autonomic disorders are apparent at birth or within the first year of life. Some of these disorders occur as a result of developmental abnormalities caused by specific genetic mutations required for neural crest cell migration and maturation; others occur as a result of prematurity or generalized central dysfunction (Table 4). Those disorders that occur as a result of biochemical errors causing neurotransmitter deficiencies or inefficient mitochondrial metabolism can be more insidious and later in their presentation. In addition, autonomic dysfunction has been noted with various disorders for which mechanisms remain obscure, such as autism and chronic fatigue syndrome (CFS), and also may be associated with various chronic diseases. Table 4 lists some of these disorders, but the list continues to expand. A few representative disorders will be described.

Autonomic Disorders Associated With Developmental Arrest or Aberrant Development of Function

Hereditary Sensory and Autonomic Neuropathies

General Description

The complexities of the ANS and its intimate relationship with sensory function is especially well illustrated in the group of genetic disorders known as hereditary sensory and autonomic neuropathies (HSANs).[6,7,20] Each HSAN disorder is probably caused by different genetic errors affecting a specific aspect of small fiber neurodevelopment and resulting in variable phenotypic expression.[6,7,20] With the exception of hereditary sensory radicular neuropathy (HSAN type I), which is a dominant disorder presenting in the second decade of life, the other HSANs are autosomal recessive disorders that present at birth. Two HSANs with specific genetic mutations are FD (HSAN type III) and congenital insensi-

TABLE 2 **CAN: Anatomy and Function**

Anatomic Area	General Function	Clinical Manifestations
Insular and medial prefrontal cortices	High-order autonomic control: input from gastric mechanoreceptors, arterial chemoreceptors, baroreceptors	Cardiac arrhythmia
Extended amygdala	Autonomic expression of emotional states: integrates autonomic and motor responses	Viscerosensory phenomena (eg, unilateral hyperhidrosis) Vomiting (left temporal focus) Sexual arousal
Hypothalamus	Homeostasis: initiates and coordinates biological rhythms, autonomic, neuroendocrine, and behavioral responses	Hypothermia or hyperthermia Poor stress response (autonomic storm) Insomnia
Midbrain	Coordinates autonomic, pain-controlling, and motor mechanisms for stress-related, aggressive, and reproductive behaviors	Hypertension or hypotension, arrhythmias Intractable vomiting and dysmotility Hypoventilation Urinary retention
Pons	Relays viscerosensory information to forebrain	
Nucleus of the tractus solitarius	Relays viscerosensory information from vagus and glossopharyngeal nerves to other CAN regions	
Medulla	Cardiovascular and respiratory control via premotor autonomic and respiratory neurons controlling input to spinal, respiratory, and preganglionic motor neurons	Sleep-disordered breathing (eg, apnea, alveolar hypoventilation)

tivity to pain with anhidrosis (CIPA or HSAN type IV). For each HSAN type, penetrance is complete, but there can be marked variability in expression. Characteristic to all HSANs is that intradermal injection of histamine phosphate fails to elicit a normal axon-flare response.[7] However, FD is the only HSAN for which there is commercially available genetic testing.

FD

In FD, the gene is *IKBKAP* (IκB kinase–associated protein gene), and >99% of individuals with FD are homozygous for a mutation in intron 20 that causes a drastic reduction in correctly spliced messenger RNA in neuronal tissue and, therefore, a lack of expression of the normal protein product IKAP (IκB kinase–associated protein).[21,22] It has been postulated that IKAP aids in expression of various neurotransmitters and that production of the abnormal gene product impedes this ability.[23] Although FD is almost exclusive to individuals of Eastern European Jewish extraction,[21,22,24] it is the most prevalent HSAN type and often used as the prototype with which to compare other HSAN disorders.[7] In FD there is inadequate development, as well as limited survival, of sensory and autonomic neurons, with the sympathetic population more widely affected than the parasympathetic population. Pathologic studies have demonstrated decreased unmyelinated and small myelinated neuronal populations in the peripheral sensory nervous system and the ANS. Although central autonomic symptoms are present, no consistent central neuropathology has yet been described.

Although patients with FD have decreased pain and temperature perception, the sensory perturbations are not as profound as in the other HSANs.[25] Bone and skin pain are diminished but not absent; sensitivity to visceral pain is intact. Corneal and tendon reflexes are hypoactive, and taste appreciation is diminished, consistent with absence of lingual fungiform papillae. With age, vibratory sensory loss and impaired coordination appear.[26]

The autonomic disturbances, however, are very prominent, involve peripheral and central tracts, and impose the greatest impediments to function, especially in the neonatal period.[7,27] In addition to absence of tears (alacrima) with emotional crying, a cardinal feature of the disorder, feeding difficulties resulting from poor oral coordination and hypotonia are frequent. Recurrent misdirection, especially of liquids, and frequent gastroesophageal reflux put the patient at risk for aspiration and chronic lung disease. Protracted episodes of nausea and vomiting can be triggered by emotional or physical stress or even arousal from sleep. These episodes, also termed the dysautonomic crisis, are usually associated with a constellation of signs including agitation, tachycardia, and hypertension. Vasomotor and cardiovascular perturbations manifest as erythematous skin blotching and hyperhidrosis with excitation or even eating. Patients can exhibit both extreme hypertension and profound and rapid postural hypotension without compensatory tachycardia.[7] Supersensitivity to cholinergic and adrenergic agents has been demonstrated.[28,29] Patients have relative insensitivity to hypoxemia,[30–33] which limits their ability to cope with pneumonia or travel to high

TABLE 3 **Functional Organization of Symptoms Associated With ANS Disorders**

System	Dysfunction	Symptom
Vasomotor/cardiovascular	Hypertension	Headache
	Hypotension	Dizziness, lightheadedness
	Arrhythmia	Loss of consciousness/syncope
	Vascular irritability	Acrocyanosis, cold hands and feet, blotching
Gastrointestinal	Oropharyngeal dysmotility	Feeding problems (poor suck, drooling, aspiration pneumonia)
	Esophageal dysmotility	Dysphagia (difficulty swallowing)
	Gastroesophageal reflux	Nausea
	Bowel dysmotility	Recurrent vomiting
		Bloating
		Profound constipation or diarrhea
Ophthalmologic	Alacrima	Dry eye
	Nonreactive/sluggish pupils	Dark/light intolerance
	Anisocoria	Severe myopia
	Ptosis	Strabismus
Respiratory	Alveolar hypoventilation	Cyanosis with sleep
	Apnea	Breath-holding spells
	Insensitivity to hypoxia	Syncope at high altitudes/plane travel
	Insensitivity to hypercarbia	
Sudomotor	Altered sweating	Hypohidrosis or hyperhidrosis
	Thermoregulatory abnormalities	Decreased basal body temperature
		Excessively dry skin
		Unexplained high fevers
Neurologic	Altered perception of pain	Sensory defensiveness
		Decreased response to injury, injections, and dental procedures
		Self-mutilation
	Sleep/wake disturbance	Insomnia
Urologic	Delayed bladder emptying	Nocturnal enuresis (>5 years of age)
Psychological	Altered affect	Poor socialization skills
	Unusual emotional responses	Increased anxiety
	Poor executive planning	Poor school performance
	Learning disability	Emotional lability
	Attention problems	Tics/phobias

altitudes. Ensuing hypoxemia may lead to hypotension, bradyarrhythmia, and even syncope. Developmental milestones are commonly delayed, but intelligence is usually within normal ranges.[34]

Although the gene has been identified, the mainstay of treatment remains preventative and supportive. These treatments have included measures to maintain eye moisture, fundoplication with gastrostomy to provide nutrition and avoid risk of aspiration, use of central agents such as benzodiazepines and clonidine to control vomiting and the dysautonomic crisis, and fludrocortisone and midodrine to combat cardiovascular lability.[7,27] As a result of improved supportive measures, approximately half of these patients now reach adulthood.[35]

CIPA

CIPA is caused by mutations in the neurotrophic tyrosine kinase receptor type 1 (*NTRK1*) gene located on chromosome 1 (1q21-q22).[36,37] As a result of loss-of-function mutations, signal transduction at the NGF receptor is impeded and NGF-dependent neurons, the small sensory and sympathetic neurons, fail to survive. There is no particular ethnic distribution for this disorder, but one half of the reported cases have occurred in consanguineous marriages.[6,7]

CIPA/HSAN type IV is characterized by anhidrosis (absent or markedly decreased sweating),[6] which is probably secondary to impaired thoracolumbar sympathetic outflow. It is the anhidrosis that causes episodic fevers and extreme hyperpyrexia that is usually the earliest sign of the disorder. Anhidrosis also contributes to the thick and calloused appearance of the skin with lichenification of palms, dystrophic nails, and areas of hypotrichosis on the scalp.[38] As evidence of parasympathetic dysfunction, patients exhibit miosis with dilute intraocular mecholyl and have mild postural hypotension. In contrast to patients with FD, emotional tearing is normal, there is no acrocyanosis, and cardiovascular responses are normal in the early years. Gastrointestinal dysmotility is infrequent; vomiting is not a feature of the disease, and cyclical crises do not occur. Insensitivity to hypoxia and hypercapnia has not been noted.

The insensitivity to pain is profound and can result in self-mutilation, autoamputation, and corneal scarring.

TABLE 4 **Pediatric Autonomic Disorders**

Etiology	Classification	Disorders	Gene
Developmental disorders	Hereditary sensory and autonomic disorders	FD (HSAN type III)	IKBKAP
		CIPA (HSAN type IV)	*NTRK1*
		Congenital sensory neuropathy (HSAN type II)	Unknown
	Allgrove syndrome		*AAAS*
	Cardiorespiratory dysregulation disorders	CCHS	*PHOX2B*
		Long-QT syndrome	6 genes (*KCNQ1*, *KVLQT1*, *HERG*, *SCN5A*, *KCNE1*, *MiRP1*)
	Chromosomal disorders	Prader-Willi syndrome	? gene/Ch15q11-q13
		Fragile X	*FMR1*/Ch X
		Rett syndrome	*MECP2*/Ch X
Biochemical errors	Myopathies	Mitochondrial myopathies: Leber hereditary optic neuropathy; X-linked kinky-hair disease; Leigh syndrome; Kerns-Sayre syndrome; myoneurogastrointestinal disorder with encephalopathy	Mitochondrial DNA point mutations
		Nemaline myopathy	*TPM3*, *NEB*
		Central core disease	Ryanodine receptor gene
	Neurotransmitter deficiencies	Dopamine β-hydroxylase deficiency	*DBH*
		Menkes	*MNK*
	Storage disorders	Fabry disease	*GLA*
	Metabolic/endocrine disorders	Diabetes	
		Addison disease/Cushing disease	
		Thyroid disorders	
Unknown	Genetic or autoimmune or postinfectious ?	Autism	
		CVS	
		Functional abdominal pain	
		CFS	
		POTS	
		Sudden infant death syndrome	
		Late-onset alveolar hypoventilation with obesity and hypothalamic dysfunction	
	Prematurity		

Although there is no immunologic problem, ectodermal structures, skin and bone, heal poorly. Fractures are slow to heal, and large weight-bearing joints seem particularly susceptible to repeated trauma and infection. Temperature sensation is also decreased or absent, but deep-tendon reflexes are usually intact. Hypotonia and delayed developmental milestones are frequent in the early years, and there can be severe learning problems, often associated with hyperactivity. For patients with CIPA/HSAN type IV, the prognosis for independent function depends on the ability to manage secondary clinical problems, especially the orthopedic issues.

Allgrove Syndrome

Allgrove syndrome is a rare autosomal recessive syndrome that was first described in 1978.[39] Initially, it was also termed the "triple-A syndrome" because it was characterized by the triad of adrenocorticotropic hormone–resistant adrenal insufficiency, achalasia, and alacrima. However, because it is now appreciated that autonomic dysfunction is also a feature, the term "4-A syndrome" has been considered more appropriate.[40,41] All components are not present in every patient, and age at onset is variable. The syndrome can present in the first decade of life with severe hypoglycemic episodes, which can cause seizures or death, or dysphagia secondary to achalasia and decreased oral secretions. However, recognition of both achalasia and adrenocorticotropic hormone insensitivity may not be appreciated until adolescence or even adulthood.[42,43] Many patients have progressive neurologic findings that consist of sensorimotor degeneration, optic neuropathy, and cerebellar features, as well as predominant abnormalities in the parasympathetic ANS.[40,41] The autonomic ocular findings include alacrima, keratoconjunctivitis sicca, lacrimal gland atrophy, pupillary abnormalities with hypersensitivity to dilute pilocarpine, and inappropriate accommodation.[43–45] Autonomic dysfunction also results in orthostatic hypotension with preservation of compensatory tachycardia and affects secretions so that sweating and oral secretions are diminished and males suffer sexual impotence.[46]

The Allgrove locus is on chromosome 12q13.[45–47] Mutations have been found in the *AAAS* gene, which codes for the WD-repeat–containing ALADIN (alacrima-achalasia-adrenal insufficiency-neurologic disorder) protein.[48] It is interesting to note that there is significant clinical variability between patients with the same *AAAS* mutation, suggesting genetic heterogeneity.

Disorders With Cardiorespiratory Dysregulation

Disorders with cardiorespiratory dysregulation as their prominent feature affect breathing control. Thus, their consequences can be fatal. One of these disorders, congenital central hypoventilation syndrome (CCHS), is described below.

CCHS was first described in 1970 and soon thereafter referred to by the literary misnomer "Ondine's curse."[49,50] It typically presents in the newborn period with cyanosis during sleep, although those who are more severely affected hypoventilate awake and asleep with resultant hypercarbia and hypoxemia.[50] With compromised ventilatory and arousal responses to hypercarbia and hypoxemia, patients do not increase their minute ventilation nor perceive the physiologic compromise from breath-holding or exercise.

The mainstay of management to optimize neurodevelopmental outcome is tracheostomy with mechanical ventilation.[50] Diaphragm pacing is a daytime alternative for the child who requires ventilation 24 hours/day or potentially a nighttime alternative for the older adolescent or young adult who requires ventilation 12 hours/day. Mask ventilation and negative-pressure ventilation are other options for the child who requires ventilation only during sleep, although the transition to mask ventilation is better delayed until the child is old enough to understand the need to wear the mask for life support.[50]

In addition to its prominent effect on cardiorespiratory regulation, children with CCHS often have symptoms of diffuse ANS dysfunction that affect heart rate and blood pressure responses, gastrointestinal motility, and other homeostatic functions including sweating and body-temperature regulation.[51–53] Altered perceptions of pain and anxiety and ophthalmologic abnormalities including strabismus, altered pupillary responses, and accommodation have been described also.[51,54–56] Although children with CCHS can experience an overall good quality of life, neurodevelopmental outcome can vary as a result of ANS dysregulation specific to CCHS or chronic/intermittent hypoxemia.[50]

CCHS is considered a unique genetic entity with diffuse autonomic dysregulation, Hirschsprung disease in ~20% of cases, various tumors of neural crest origin in ~5% of cases, and characteristic facies.[54,57–59] Individuals with the CCHS phenotype are heterozygous for a *PHOX2B* gene mutation located on chromosome 4p12.[60–64] In 90% to 95% of CCHS cases there is a polyalanine expansion mutation in exon 3, and in 5% to 10% of cases there is a unique mutation. A relationship between polyalanine-repeat length and the severity of autonomic dysfunction, as indicated by the number of associated autonomic symptoms, has been noted.[62,64] Subjects with unique mutations in *PHOX2B* have a higher rate of Hirschsprung disease, higher frequency of ventilation requirement for 24 hours/day, and more frequent neural crest tumors than in the polyalanine expansion-mutation group.[61,62,64–66]

A polymerase chain reaction–based DNA test is clinically available for diagnosis of CCHS. This test can be used to identify probands and the presence of mosaicism in parents and for prenatal diagnosis. The assay also has applicability in diagnosing CCHS in adults with unexplained hypercarbia or control of breathing deficits.[67]

Chromosomal Disorders

Chromosomal disorders usually have multisystem perturbations, and it is increasingly appreciated that autonomic dysfunction can be a feature of many of these disorders because of either expansions or deletions of particular genes. One illustrative disorder is Rett syndrome.

Rett syndrome is a neurodevelopmental disorder that predominantly affects females. Mutations in the gene encoding methyl-CpG-binding protein 2 (*MECP2*) on the X chromosome have been identified in 95% of girls with the Rett syndrome phenotype.[68,69] The diagnosis is based on clinical criteria.[70] The phenotype typically includes normal development until 6 to 18 months of age, and then there is regression with slowing of head circumference growth, loss of language, development of stereotypical hand movements, and gait and truncal apraxia. Some girls also develop electroencephalogram abnormalities, seizures, spasticity, and scoliosis.

The autonomic features include cardiorespiratory dysregulation and abnormal blood pressure responses. Respiratory dysregulation includes hyperventilation, apnea, breath-holding, and rapid shallow-breathing.[71–82] During wakefulness, breathing dysrhythmias are associated with agitation or excitement as well as other motor functions. During sleep, polysomnography has documented increased frequency of desaturation events and periodic breathing. Girls with Rett syndrome who demonstrate hypoxemia without hypercarbia, awake or asleep, should be treated with supplemental oxygen. Likewise, girls who demonstrate evidence for obstructive sleep apnea (without a treatable cause) should be treated with mask bilevel positive airway pressure during sleep. In so doing, the girls will be protected from the sequelae of acute and chronic intermittent hypoxemia and hypercarbia.

An imbalance of sympathovagal input has been reported.[77,81] Decreased cardiac vagal tone and cardiac sensitivity to baroreflex have been identified and result in unopposed sympathetic activity with extreme hypertension and tachycardia. Additional support for autonomic dysregulation comes from observations of decreased heart rate variability, prolongation of corrected QT intervals, and sinus bradycardia.[83–86]

Despite survival into adulthood, 26% of all deaths from Rett syndrome are sudden and unexpected, and cardiac causes for sudden death have been suggested

because of autonomic dysregulation.[82,86,87] Additional assessment of heart rate variability and control of breathing is needed to elucidate the mechanisms involved in sudden death.

Autonomic Disorders Associated With Biochemical Errors

Mitochondrial encephalomyopathies are heterogeneous multisystem disorders characterized by structural or biochemical defects in the mitochondria that impair normal oxidative phosphorylation.[88] Common symptoms include hypotonia, ophthalmoplegia, seizures, pyramidal and extrapyramidal signs, psychomotor regression, ataxia, stroke-like episodes, lactic acidosis, and sometimes endocrinopathies.[88,89] In general, involvement of the ANS has not been stressed; however, on occasion, the autonomic abnormalities can be so severe that they can overshadow the myopathic features and may delay definitive diagnosis.[89] Autonomic features including vomiting, impaired respiratory control, and cardiac arrhythmia have been observed with Leigh syndrome and Kerns-Sayre syndrome and in myoneurogastrointestinal disorder with encephalopathy.[90–92] In addition, autonomic or visceral features such as cardiac conduction defects or hypothermia and feeding problems may occasionally occur in other mitochondrial diseases including Leber hereditary optic neuropathy[93] and X-linked recessive kinky-hair disease.[94] In addition, decreased lacrimation, vasomotor disturbances characterized by blotchy erythema and skin mottling, altered sweating, and postural hypotension have also been noted in individuals in whom muscle biopsy has verified abnormal respiratory-chain enzymes.[89]

Because mitochondrial disorders are multisystem diseases, dysfunction of the ANS may be a result of structural abnormalities of mitochondria within the central or peripheral nervous system.[95] Diagnosis is verified by biochemical assays for mitochondrial enzyme activities.

Unknown

Autism

Autism is a complex neurodevelopmental disorder that produces social, behavioral, and language impairment. Approximately three quarters of the children with autism have mental retardation, and one third have seizures. It affects more males than females.[96] However, in addition to traditional neurodevelopmental symptoms, it is now appreciated that autism also produces symptoms attributable to other organ systems. Some of these manifestations, including unexplained constipation or diarrhea, urinary retention, cold and clammy extremities, and sleep disturbances, suggest underlying autonomic dysfunction.[97] These children seem to have impaired parasympathetic activity resulting in unrestrained sympathetic activity.[97] Autonomic tests have demonstrated blunted autonomic arousal responses to visual and auditory social stimuli.[98,99] In addition, there is low baseline cardiac vagal tone and low cardiac baroreceptor sensitivity, resulting in hyperactive heart rate and blood pressure responses.[97] However, paradoxically, children with autistic behavior are less flexible in their autonomic adaptation to attention-demanding tasks and demonstrate less decrease in heart rate variability than normal controls during periods of task performance.[97]

In support of central autonomic dysfunction, pathologic examinations have revealed abnormalities in central structures often associated with autonomic control, such as the brainstem, the amygdala, the limbic system, the cerebellum, and the prefrontal lobes.[100] In addition, abnormal levels of monoaminergic and cholinergic neurotransmitters, including norepinephrine, dopamine, acetylcholine, serotonin, and various neuropeptides, have been reported.[97] In addition, secretin and oxytocin, both polypeptide neurotransmitters that cross the blood-brain barrier, have each been reported to improve some of the symptoms in different autistic subgroups.[101,102] The reversal of symptoms through agents that seem to alter central autonomic function further supports direct involvement of autonomic centers in autism.

Functional Gastrointestinal Disorders

By definition, in functional gastrointestinal disorders, there are no anatomic, inflammatory, or biochemical abnormalities to explain the symptoms.[103] Although their pathophysiology is generally unknown, it is hypothesized that the interaction between specific psychosocial factors and gut innervation through the brain-gut axis, including both neuroendocrine and ANS, may produce an abnormality of gut function. The gut dysfunction may be expressed by abnormal motility, visceral hyperalgesia, or both.

The functional gastrointestinal disorders of childhood are classified according to the ROME II criteria in 4 groups and several subgroups.[104] The groups include (1) vomiting, (2) abdominal pain, (3) functional diarrhea, and (4) disorders of defecation. Although all of these may be associated with autonomic dysfunction, the evidence is clearest for cyclic vomiting syndrome (CVS) and functional abdominal pain.

CVS

CVS is characterized by severe, discrete episodes of nausea, vomiting, and lethargy of unclear etiology, with baseline return to health between episodes.[105–107] It is predominantly a disease of childhood, affecting ~1.9% of school-aged children and frequently evolves into migraine headaches in adulthood.[105] Episodes often are triggered by emotional or physical stress, during which many autonomic symptoms are exhibited, including increased salivation, pallor, increased sweating, nausea, increased blood pressure, diarrhea, and dizziness.[107,108] A

prodrome of headaches, photophobia, or vertigo often precedes the period of vomiting.[105–108] Autonomic testing has demonstrated abnormalities characterized by increased sympathetic modulation as reflected in heart rate variability and postural intolerance.[109,110] Although some consider CVS to be a migraine variant, these studies suggest an autonomic basis.[110] The cause of CVS is unknown, but genetic factors have been suggested, because a subset of children with CVS seems to have maternal inheritance and an associated mitochondrial DNA variation.[111]

Functional Abdominal Pain

The association of functional abdominal pain and autonomic dysfunction in children is still poorly understood. It is not uncommon for children with functional gastrointestinal disorders to report various autonomic symptoms including dizziness, headaches, flushing, sweating, Raynaud's phenomena, and severe fatigue.[112] In addition, in a subset of children with functional abdominal pain, postural orthostatic tachycardia syndrome (POTS) and mild peripheral neuropathy have been noted.[113] An operational definition of POTS includes symptoms of orthostatic intolerance, such as fatigue, light-headedness, nausea, vomiting, headache, palpitations, and tremulousness, associated with increased heart rate exceeding 30 beats per minute or to a heart rate >120 beats per minute within 10 minutes of head-up tilt.[114] Thus, patients with POTS also report a variety of gastrointestinal symptoms such as nausea, bloating, early satiety, abdominal pain, and other gastrointestinal manifestations.[115] Furthermore, patients with functional abdominal pain often respond favorably to treatments directed toward ANS dysfunction such as relaxation and guided imagery and medical treatment such as increasing dietary salt, fludrocortisone, and β blockers.[115]

CFS

CFS is now recognized as a distinct disorder with specific diagnostic criteria.[116] It is characterized by chronic or relapsing fatigue, lasting for at least 6 months, causing impaired overall physical and mental functioning. Often there is a paucity of physical findings resulting in CFS being a diagnosis of exclusion. Self-reported symptoms can include cognitive difficulties, muscle pain, joint pain, headache, sleep disturbance, poor sleep, and postexercise malaise, as well as a variety of gastrointestinal symptoms.[116–118]

Onset of symptoms often follows an infectious disease and may be related to inflammatory mediators.[119,120] According to a report generated from a Centers for Disease Control and Prevention workshop,[116] pediatric CFS patients are mostly teenage females who report a preceding inflammatory condition. Similar to the adult experience, orthostatic intolerance in adolescents with CFS is consistent with POTS.[118,121] CFS may represent a severe form of POTS in adolescents, and the autonomic findings may be related to circulatory abnormalities at rest and during orthostasis. Stewart et al[121] have demonstrated loss of heart rate variability consistent with vagal withdrawal, increased blood pressure variability consistent with enhanced modulation of sympathetic tone, and impaired baroreflex.

Because no cause for CFS has been identified and the pathophysiology remains unknown, treatment programs are directed at relief of symptoms, with the goal of the patient regaining some level of preexisting function and well-being. Nonpharmacologic therapies include light exercise and patient education. Pharmacologic therapy is directed toward the relief of specific symptoms experienced by the individual patient. Fludrocortisone has been prescribed for patients with CFS who have had a positive tilt-table test, but it may need to be combined with other treatments such as midodrine, an agent that directly increases blood pressure, as well as increased salt and water intake.

EVALUATION AND THERAPEUTIC INTERVENTIONS

It is beyond the scope of this article to give extensive descriptions of the various diagnostic techniques that can be used to differentiate and characterize the various autonomic disorders. In addition, there is still a need to reach consensus among investigators as to which techniques provide the most accurate means of assessment in the pediatric population. To this end, the American Autonomic Society created a task force for the specific purpose of providing a consensus statement regarding assessment guidelines.

In the interim, it is recommended that evaluation of the child suspected of having autonomic dysfunction start with a comprehensive history and be accompanied by a clinical examination that focuses on neurologic features. Questions and examination should attempt to discern if the problem is static or progressive, if there are peripheral and/or central autonomic disturbances, if there are associated sensory problems, and if there is muscle weakness. Because decreased response to pain can be caused by emotional indifference, as well as true insensitivity resulting from neuronal dysfunction, the response to particular injuries should be documented. Although the indifferent patient might not respond to a fall or laceration, the response to a fracture or a burn is expected to be appropriate, because deep pain fibers are intact. Objective tests also can be performed to verify neurologic dysfunction, such as the histamine test and the sympathetic skin response. The intradermal histamine test still remains a good screening test for sensory dysfunction caused by small-fiber neuropathy, and an abnormal response (ie, absence of the axon flare) can be seen in all the HSAN types.

To further assess autonomic dysfunction and identify

sympathetic or parasympathetic deficits, a few relatively simple "bedside" tests can be performed. Active standing or a passive head-up tilt evaluates orthostatic cardiovascular control. For a detailed description of other autonomic tests that are used in the adult population, such as metronomic breathing (which challenges parasympathetic cardiovascular modulation) and the Valsalva maneuver (which tests baroreflex buffer capacity and reflex bradycardia), the reader is referred to standard textbooks.[2–4] However, many of these tests cannot be administered to the pediatric patient, for whom we desire noninvasive quantitative tests that require minimal participation and cooperation.

Although gene identification holds the promise of eventually yielding more specific treatments for some of the autonomic disorders, at present most treatments are supportive. If the autonomic perturbations seem to involve only one organ system, then it is reasonable that evaluation and therapy decisions will be system specific. In some instances, the treatments that have been found effective in the genetic autonomic disorders such as the HSANs (in particular, FD) have been tried in the other autonomic disorders. For episodic signs of central sympathetic storm that include symptoms such as tachycardia, hypertension, diaphoresis, and hyperpyrexia, central α agonists such as clonidine have been tried. However, when there is multisystem involvement, then a more comprehensive assessment with careful evaluation of the autonomic and sensory systems is warranted, because choices for therapeutic interventions can be complicated and treatment for one system may provoke perturbations in another. In such cases, a comprehensive approach is needed for optimal management.

CONCLUSIONS

The ANS innervates every organ in the body, and thus its effects are pervasive and perturbations can cause a broad spectrum of symptoms. The list of pediatric disorders with autonomic dysfunction, primary or secondary, is continuing to expand. Therefore, to increase our diagnostic acumen in this area and develop better treatments, it is essential that we better understand the ANS, its normal functioning, and the role of its various components.

The goal of this review is to promote awareness of ANS disorders that affect the pediatric population. We are not describing new disorders; rather, we are providing a new perspective on a number of well-recognized pediatric disorders, which may lead to innovative treatment approaches such as correcting neurotransmitter imbalances. We are continuing to learn about the various signs and symptoms of autonomic dysfunction in the young child, and there still remains a need for ongoing research into the genetics and pathophysiology of the various disorders and consensus regarding techniques for objective assessment of autonomic and sensory function in the pediatric population.

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PRESCRIPTION-DRUG USE BY TEENS

"While teen smoking and drinking continue to drop, a new survey indicates that teenage abuse of prescription drugs has become 'an entrenched behavior.' For a third straight year, the Partnership for a Drug-Free America study showed that about one in five teens has tried prescription painkillers like Vicodin or OxyContin to get high—about 4.5 million teens. It also indicated that many teens feel experimenting with prescription drugs is safer than illegal highs. Forty percent said prescription medicines were 'much safer' than illegal drugs; 31% said there was 'nothing wrong' with using prescription drugs 'once in a while.' "

Associated Press. May 16, 2006
Noted by JFL, MD