Biogenic amine metabolism in juvenile neurocardiogenic syncope with dysautonomia

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Abstract

Objective: Biogenic amine brain levels and their cerebral metabolism are frequently studied by quantitation of biogenic amine metabolites in cerebrospinal fluid (CSF) compared to age-matched controls. There is a paucity of studies in adolescents and young adults investigating the potential role of disordered cerebral biogenic amine metabolism in young patients who have dysautonomia based on abnormal head-up tilt table (HUTT). Methods: In a cohort of juvenile patients with neurocardiogenic syncope and dysautonomia documented by abnormal HUTT, biogenic amine metabolites of dopamine and serotonin were quantitated in 18 patients (15 females). HUTT testing is an effective clinical method to evaluate posturally induced physiological events in patients suspected of neurocardiogenic syncope with dysautonomia. Results: Levels of the dopamine metabolite (homovanillic acid: HVA) and/or the serotonin metabolite (5-hydroxyindoleacetic acid: 5HIAA) were significantly reduced in 13 patients compared to age-matched controls. Interpretation: Peripheral biogenic amines and their metabolites have been extensively studied in adults with dysautonomia due to various neurodegenerative disorders (Parkinson disease, multiple system atrophy, primary autonomic failure). Our findings indicate that more than two-thirds of this cohort of young patients with dysautonomia of variable severity have a defect in cerebral biogenic amines, particularly in dopamine and serotonin metabolism.

Introduction

Orthostatic intolerance with neurocardiogenic syncope and clinical features of dysautonomia are considered a disorder of the autonomic nervous system with abnormal physiological response of the sympathetic and parasympathetic nervous system components often precipitated by upright posture (sitting or standing) and by exercise or other physical stress. Clinical manifestations of orthostatic intolerance are observed frequently in children, adolescents, and young adults and in older subjects.¹ Usually there is not an apparent neurological disorder in children and young adults, unlike older subjects where secondary medical and neurological conditions such as diabetes mellitus with neuropathy, various acquired and genetic peripheral neuropathies and degenerative brain disorders (multiple system atrophies, Parkinson disease) are present. Patients with autonomic nervous system dysfunction manifest with one or more clinical manifestations. Investigators previously described symptoms of orthostatic intolerance, fatigue, postural tachycardia, dizziness, and syncope as secondary to sympathetic/parasympathetic imbalance and/or attenuated vagal baroreflex.²,³ This syndrome has been labeled by several investigators as “dysautonomia” or autonomic dysfunction.⁴,⁵ Dysautonomia can cause symptoms related to the nervous system (dizziness, syncope, “brain fog,” migraine headaches), cardiac system (palpitations, chest pain, hypotension), gastroenterologic system (low/high intestinal motility, nausea, abdominal functional pains), urinary symptoms (frequent urination, hesitination), skin manifestations (clamminess, pallor, hot/cold intolerance), and musculoskeletal disorders (fatigue, muscle aches, and inability to exercise). The term dysautonomia describes the above syndrome more appropriately than other terms such as vasovagal
syncope, postural orthostatic tachycardia syndrome (POTS), or neurally mediated syncope.\textsuperscript{2}

In our detailed studies of a large cohort of more than 400 adolescents and young adults (age 7–30 years) with clinical manifestations of postural intolerance with neurocardiogenic syncope, we have documented by head-up tilt table testing (HUTT) that these subjects have dysautonomia.\textsuperscript{6} Many subjects were evaluated by pediatric neurologists for severe and incapacitating headaches that were frequent and persistent such that further neurological studies were necessary, including neuroimaging (computed tomography or magnetic resonance imaging) and a diagnostic lumbar puncture with opening cerebrospinal fluid (CSF) pressure to exclude raised intracranial pressure syndrome. Of these, more than 400 subjects studied by HUTT, we evaluated a cohort of 18 adolescents and young adults who were selected based on our previous observation of abnormal biogenic amine neurotransmitter metabolites in CSF from several subjects with postural intolerance being assessed for neurometabolic conditions.\textsuperscript{7}

**Patients and Methods**

Retrospective analysis of 18 children and adolescents who had CSF examination and symptoms of dysautonomia were included in this study. Subjects were 12.5–20.5 years of age with seven subjects between 10–15 years and 11 subjects who were 16 years and above (adults). Fifteen of the 18 subjects were female. Subjects were referred to our institution for neurologic or cardiology consultation for migraine-like headaches and seizures, syncope and/or presyncope, palpitations and chest pain, episodes of visual loss, or with other clinical complaints such as abdominal and back pain, chronic fatigue and acrodysesthesias, postural and/or exercise intolerance, or severe muscle pain and weakness. Subjects completed a comprehensive clinical questionnaire designed to quantify the severity of their protean clinical manifestations.

In our center, HUTT was performed with continuous recording of measured cardiac stroke volume (via transthoracic impedance), systolic and diastolic blood pressure and heart rate, using Task Force Monitor\textsuperscript{8} (Graz, Austria). Sympathetic and parasympathetic activity was calculated from heart rate and diastolic BP variability by Fourier harmonic analysis. Additionally, subjects had monitoring of bilateral cerebral blood flow by near-infrared regional spectroscopy (NIRS) utilizing Nonin\textsuperscript{9} monitor (Minneapolis, MN). Monitoring occurred during the initial resting supine phase (5 min), during the head-up tilting to an angle of $70^\circ$ (for a period not exceeding 30 min), and the recovery phase following slow return to supine phase (10 min). All subjects had an intravenous line placed and a registered nurse and a pediatric cardiologist were in attendance during all phases of the HUTT. Symptoms and signs of dysautonomia were monitored and recorded by the attending physician. The study was discontinued before 30 min in the presence of severe symptoms, request of the subject (due to inability to continue), or with the recommendation of the attending physician. Severe and critical clinical manifestations of dysautonomia included hypotension, bradycardia, overwhelming nausea or vomiting, syncope, seizure-like activity, and occasional asystole (for $>3$ sec duration). Postural intolerance during HUTT was recorded in minutes in subjects who did not complete 30 min of tilting (Table 1).

CSF was collected and transported on dry ice in small tube aliquots at the time of a diagnostic lumbar puncture to measure CSF pressure for evaluation of patients with severe and/or daily headaches in order to exclude raised intracranial pressure syndrome or other posturally related headaches. These patients were also being assessed for postural intolerance and had a positive HUTT. CSF by routine biochemical and cell count analyses were normal in all subjects. High performance liquid chromatography–electrochemistry methods were utilized to quantitate 5-hydroxyindoleacetic acid (5HIAA), homovanillic acid (HVA), 3-O-methyldopa, neopterin (NEO), tetrahydrobiopterin (THBiopt), 5-methyltetrahydrofolate, succinyladenosine, and pyridoxal 5-phosphate levels\textsuperscript{8} and compared to age-related reference values.\textsuperscript{9}

Descriptive analyses (median and interquartile range, IQR) were performed for all the initial metabolite levels and number of minutes before discontinuation of HUTT. Subjects were classified as “low metabolite” or “normal metabolite” based on whether the serotonin and/or dopamine metabolite levels in CSF were below age-related normative values or not, respectively. Pairwise correlation coefficients were calculated for all metabolites. Mann–Whitney rank-sum tests were used to compare time to discontinuation of HUTT between the “normal” and “low” metabolite level groups (initial study with both metabolite and HUTT data points was utilized for this analysis). All statistical analysis was performed using STATA (v.10; College Station, TX). Statistical significance was assumed at $P < 0.05$.

**Results**

All 18 subjects with clinical features of neurocardiogenic syncope with dysautonomia were confirmed to have significant abnormalities by HUTT. Results from the CSF and HUTT studies for all patients are listed in Table 1. The data for patient 13 were not included in the analysis as her studies were performed posttreatment with levodopa.
The CSF metabolite levels for dopamine (HVA) and/or serotonin (5HIAA) were below the age-related reference values in 12 (71%) subjects (i.e., “low metabolite” group): 10 (59%) with decreased levels of both metabolites and one each with low levels of only dopamine and only serotonin metabolites. Levels that were within age-related norms for both dopamine and serotonin metabolites were present in five (30%) subjects (i.e., “normal metabolite” group) (Fig. 1).

The median metabolite levels for each metabolite are listed in Table 2. There was a strong-to-moderate correlation between dopamine and serotonin metabolite levels ($r = 0.76$, $P < 0.001$) and dopamine and tetrahydrobiopterin metabolite levels ($r = 0.54$, $P = 0.002$).

Three of the subjects (subjects 5, 7, and 9) had sequential CSF studies performed 1–5 years after the initial study. The first and second serotonin metabolite levels were comparable in all three of these subjects, while dopamine metabolite levels were comparable in only two subjects. The other subject (subject 9) had a significant decrement in her dopamine metabolite levels over the 5-year interval between her CSF studies. During that period, her levels decreased from what would be considered “normal” based on reference values to “low”. This subject also had the longest interval (5 years) between her two measurements compared to the other two subjects (1–2 year intervals).

Although abnormalities in HUTT were observed in all subjects, the studies were discontinued prematurely in 10 subjects (59%). The median time to discontinuation of HUTT was significantly lower in subjects with low levels of serotonin and/or dopamine metabolites than those with normal levels (15.5 min, IQR: 4.5–28.5 vs. 30 min, IQR: 30–30; $P = 0.049$). Interestingly, only one subject (20%) among those with normal metabolite levels failed to tolerate the HUTT for the full 30 min, compared to nine (75%) among those with low metabolite levels.

### Illustrative Cases

#### Subject 6

A young female of 14.5 years of age was evaluated for a long-standing history of throbbing occipital headaches that occur every other day with photophobia and persisting for more than 4 h. She had palpitations with dizziness

| Subject | Age (years) | Gender | 5HIAA | HVA | FOLATE | NEO | THBiopt | HUTT (mins) |
|---------|-------------|--------|-------|-----|--------|-----|---------|-------------|
| 1       | 17          | F      | 39    | 122 | 38     | 9   | 14      | 30          |
| 2       | 16          | F      | 37    | 94  | 83     | 7   | 13      | 3           |
| 3       | 16          | F      | 39    | 107 | 63     | 8   | 16      | 30          |
| 4       | 15          | M      | 46    | 157 | 69     | 8   | 13      | 11          |
| 5a      | 17          | F      | 49    | 112 | 83     | 14  | 20      | 5           |
| 5b      | 19          | F      | 54    | 91  | 33     | 11  | 19      | 30          |
| 6       | 14.5        | F      | 57    | 132 | 52     | 13  | 14      | 2.5         |
| 7a      | 16          | F      | 42    | 114 | 61     | 9   | 13      | 30          |
| 7b      | 17          | F      | 52    | 141 | 50     | 9   | 17      | NP          |
| 8       | 17          | F      | 64    | 95  | 42     | 16  | 12      | 27          |
| 9a      | 12.5        | F      | 59    | 200 | 7      | 14  | 31      | NP          |
| 9b      | 17.5        | F      | 53    | 106 | 79     | 18  | 20      | 4           |
| 10      | 19          | F      | 72    | 139 | 49     | 17  | 25      | 10          |
| 11      | 15.5        | F      | 42    | 137 | 55     | 17  | 25      | 10          |
| 12      | 17          | F      | 63    | 114 | 75     | 17  | 18      | 20          |
| 13      | 20.5        | F      | 60    | 207 | 67     | 21  | 18      | 30          |
| 14      | 16          | F      | 95    | 212 | 68     | 12  | 28      | 30          |
| 15      | 14          | M      | 81    | 317 | 47     | 13  | 56      | 14          |
| 16      | 16.5        | F      | 114   | 236 | 71     | 8   | 19      | 30          |
| 17      | 13.5        | F      | 91    | 265 | 110    | 14  | 21      | 30          |
| 18      | 12.5        | M      | 108   | 291 | 64     | 5   | 17      | 30          |
| Control | 10–15       |       | 67–189| 167–563| 40–120 | 8–33 | 9–32   |

NP, not performed; 5HIAA, 5hydroxyindole acetic acid; HVA, homovanillic acid; NEO, neopterin; THBiopt, tetrahydrobiopterin; HUTT, head-up tilt table test.

1Post dysautonomia treatment.

2Post levodopa treatment (not included in analysis).
during exercise (school marching band) and syncopal episodes. She had a history of ligamentous laxity with an elbow dislocation. Her neurological examination was normal and magnetic resonance brain imaging and electrocardiography were normal. She failed to respond adequately to migraine prophylaxis (amitriptyline) and headache rescue with a triptan. A paternal aunt has migraine headaches.

A diagnostic lumbar puncture was performed with an opening pressure of 16 cm of water with normal routine analyses, however, there was a significant decrease in CSF dopamine and serotonin metabolites (subject 6). Her HUTT was strongly positive with a dramatic decrease in systolic blood pressure from 103 to 52 mmHg and tachycardia from 62 to 110 bpm with tilting. There was a decrease in cerebral blood flow on near-infrared spectroscopy (NIRS) and she had a clinical “blackout” and convolution at 3 min of tilting with recovery over several minutes with supine positioning. Following demonstration of an atrial septal defect with right-to-left shunting on echocardiography and on intracranial Doppler ultrasonography (double-bubble test), she had endovascular closure of her cardiac defect. At recent follow-up at 6 months after her endovascular procedure, there has been significant clinical improvement with no further migraine-like headaches nor syncopal events while on fludrocortisone 0.1 mg tid with fluid and electrolyte supplementation and antigravity exercise maneuvers.

**Subject 8**

A young female of 16 years of age was evaluated for pulsating frontal headaches for 3 years associated with palpitations, nausea, and dizziness with photophobia and blurred vision and a visual sensation of “blacking out” on standing. There was a strong family history of migraine headaches (mother, sister, and paternal grandfather). Computed tomographic imaging of paranasal sinuses and magnetic resonance brain imaging were both normal and she failed to respond to migraine headache rescue (triptan) and prophylactic (topiramate) medications. Her neurological examination was normal, including fundoscopy. Tilt table test (HUTT) was abnormal with onset of tachycardia, shortness of breath, nausea, headache, stomach ache, trembling, and hypotension (decrease in systolic

![Figure 1. Biogenic amine metabolite levels of dopamine (homovanillic acid: HVA) and serotonin (5-hydroxyindoleacetic: 5HIAA) were measured in cerebrospinal fluid by high performance liquid chromatography–electrochemistry methods in patients with dysautonomia and compared to age-related reference values.9](image-url)

**Table 2.** Comparison of minutes to discontinuation of HUTT and metabolite levels between subjects with “normal” and “low” cerebrospinal fluid metabolite levels.

|                    | Metabolite levels in CSF |
|--------------------|--------------------------|
|                    | Low (n = 12)             | Normal (n = 5) | P = value |
| HUTT, min (IQR)    | 22 (10–30)               | 15.5 (4.5–28.5) | 30 (30–30) | 0.049 |
| Metabolite levels, |                         |                |           |
| median (IQR)       |                         |                |           |
| 5HIAA              | 59 (42–81)               | 47.5 (40.5–61) | 95 (91–108) | 0.002 |
| HVA                | 137 (114–212)            | 118 (109.5–138)| 265 (236–291)| 0.002 |
| Neopterin          | 13 (8–14)                | 13.5 (8.5–16.5)| 12 (8–13) | 0.265 |
| Folate             | 63 (49–71)               | 58 (45.5–72) | 68 (64–71) | 0.252 |
| THBiopt            | 18 (14–21)               | 15 (13–20) | 21 (19–28) | 0.057 |

HUTT, head-up tilt table test; IQR, interquartile range; 5HIAA, 5-hydroxyindole acetic acid; HVA, homovanillic acid; THBiopt, tetrahydrobiopterin. Bold values denote clinical significance (P < 0.05).
blood pressure from 110 to 60 mmHg) with recovery on return to supine position. Subsequent cardiac catheterization with Valsalva maneuver and injection of agitated saline with echocardiography and transcranial Doppler ultrasonography of bilateral middle cerebral arteries (double-bubble technique) demonstrated right-to-left shunting via an atrial septal defect that was endovascularly closed. Despite management with fluid and electrolyte supplements with fludrocortisone 0.1 mg bid and amitriptyline 50 mg daily, headaches have persisted and she developed obscurations of vision such that a diagnostic lumbar was performed with normal opening CSF pressure of 16 cm of water. CSF constituents were normal, however, serotonin (5HIAA) and dopamine (HVA) metabolite levels were decreased, whereas other metabolites were normal (subject 8).

At 17 years of age, she had twice weekly episodes of tinnitus (high-pitched ringing sound), paresthesias (numbness and tingling sensation) of her fingers and toes, visual disturbances (scotomas and television snow – like auras), abdominal pain, and intolerance of increased ambient temperatures.

At a recent assessment, she complained of fatigue and headaches while on fludrocortisone 0.1 mg tid, midodrine 2.5 mg bid and propranolol 60 mg daily. There have been no further syncopal episodes nor chest pains with palpitations nor dyspnea. She is, however, no longer a competitive swimmer but maintains excellent grades at school.

**Subject 12**

A young female of 17 years of age was evaluated following a 2-week exacerbation of headaches, dizziness, abdominal pain, and numbness of her hands. Bifrontal and temporal headaches associated with postural intolerance had been present for several months. Her postural dizziness and “brain fog” prevented her from attending school. Two years earlier she was evaluated for occipital headaches and suboccipital posterior fossa decompression surgery was performed for a Chiari malformation and syringomyelia as demonstrated on magnetic resonance neuroimaging. To evaluate this exacerbation of her headaches, magnetic resonance imaging of her craniocervical junction was performed and a diagnostic lumbar puncture showed an opening pressure of 8 cm of water. Despite two epidural blood patching procedures for possible hypovolemic CSF syndrome with postural headaches, there was minimal improvement in her headaches. Her neurological examination was normal other than unsteadiness on tandem gait. Computed tomographic myelography demonstrated perineural opacification of L2 and L3 lumbar nerve roots with early opacification of the renal collecting system, although her opening CSF pressure was now normal at 16 cm of water. Subsequently, a third blood patch was placed in the lumbar epidural space. Routine CSF studies were normal; however, her dopamine and serotonin metabolites were decreased (subject 12). Tilt table testing (HUTT) was strongly positive with postural tachycardia, dizziness, light-headedness and nausea with abdominal pain, deep breathing, and a feeling of faintness. Cerebral blood flow (NIRS) decreased with 50–60% decrease in cardiac stroke volume. HUTT was terminated at 20 min with rapid recovery to baseline on supine positioning.

Following institution of fludrocortisone 0.1 mg bid and fluid and electrolyte supplementation, there have been no further presyncopal events with dramatic improvement in her headaches, fatigue, chest pain, palpitations, leg cramps, and hot/cold ambient temperature intolerance. Cardiac evaluation and endovascular closure of her atrial septal defect by echocardiography has been deferred given her clinical progress on oral hydration and fludrocortisone management.

Of interest, her mother has migraine headaches and her father has vasovagal syncope with positive tilt table testing.

**Discussion**

Our study elaborates on the association (and probably the role) of biogenic amine deficiencies relative to severe dysautonomia symptoms in children and adolescents. We have shown defects in brain dopamine and serotonin by measurement of their respective metabolites (HVA and 5HIAA) in CSF in a small selected patient subset from more than 400 patients studied in our Dysautonomia Center. Of the 18 subjects studied, 12 had decreased HVA and/or 5HIAA levels with two subjects having a decrease in one or the other CSF metabolite. There did appear to be evidence for internal metabolite stability in that three subjects had similar sequential 5HIAA levels at 1–5 years intervals (subjects 5, 7, 9) and two had stable HVA levels at 1–2 years intervals (subjects 5, 7). One subject, who also has central nervous system folate deficiency on folic acid therapy7 had a 50% decrease in HVA over 5 years (subject 9). The pathogenesis of a defect in brain dopamine and serotonin in a significant proportion (71%) of a selected subset of adolescents and young adults with clinical and tilt table evidence of neurocardiogenic syncope with dysautonomia is not readily apparent, however, various potential mechanisms could be considered.

The importance of the biogenic amines (dopamine, norepinephrine, and serotonin) in human brain disorders was initially demonstrated in postmortem histologic and
biological studies of brain tissue and CSF in patients with Parkinson disease in the early to mid 1960s.\textsuperscript{10,12} Such studies have been instrumental in our understanding of the pathogenesis and treatment of parkinsonism due to degenerative and biochemical disorders of the human brain.

Although a neurodegenerative process with defects in brain dopamine and serotonin could be indicated by decreased levels of their respective metabolites in CSF, these young subjects did not demonstrate clinical features of Parkinsonism as observed in patients with juvenile Parkinsonism. Furthermore, many of our subjects with dysautonomia have been observed clinically (either directly or by history) for multiple years without onset of Parkinsonism. One young adult (subject 9) had biochemical evidence over 5 years of a progressive deficiency of brain dopamine but without clinical features of Parkinsonism. Of interest, specific serotonin reuptake inhibitors (SSRIs) have been used for many years in the management of neurocardiogenic syncope and dysautonomia and could suggest a specific deficiency in brain serotonin.\textsuperscript{13} Thus, this study showing decreased serotonin metabolite CSF levels in a significant proportion of youngsters with dysautonomia may partially explain the clinical role of SSRIs in this disorder.

Specific neurometabolic defects in the biogenic amines have been studied since the mid 1970s with the demonstration of defects in dopamine, norepinephrine, and serotonin in brain and CSF studies of youngsters with atypical phenylketonuria.\textsuperscript{14,15} However, unlike these defined neurometabolic disorders, CSF metabolic profiles (biomarkers) in our subjects did not have decreased levels of biopterin metabolites (NEO and tetrahydrobiopterin) except a marginal decrease in NEO in one patient (subject 2). Generally, in metabolic disorders of biosynthesis and regeneration of tetrahydrobiopterin with defects in biogenic amines and their metabolites, there are also defects in CSF NEO and biopterin metabolite levels.\textsuperscript{8,9}

In addition to primary inherited disorders in biogenic amine biosynthesis in brain as studied by CSF levels of biogenic amine and biopterin metabolites, there are secondary abnormalities of these brain neurotransmitters due to other genetic disorders.\textsuperscript{8} In an early study of biogenic amines in Rett syndrome, decreased levels of biogenic amine metabolites of dopamine, serotonin, and norepinephrine were demonstrated in CSF from children with that disorder.\textsuperscript{16,17} These CSF studies were performed a decade before the demonstration of mutations in the MeCP2 gene\textsuperscript{18} as the basis for most cases with the Rett phenotype. Subsequent studies of biogenic amine metabolism in brain in Rett syndrome were inconsistent until about a decade later, a large cohort of Rett syndrome patients (64 subjects) were studied by clinical and molecular methods.\textsuperscript{19} The original findings of defective biogenic amine metabolism in a significant proportion of Rett syndrome subjects was confirmed and molecular animal studies utilizing severe and less severe human MeCP2 mutations strongly indicated the role of the MeCP2 gene in controlling neuronal specific genes and/or molecules involved in biogenic amine biosynthesis and related behavioral changes. Given the frequent familial nature of neurocardiogenic syncope and dysautonomia\textsuperscript{20}, detailed molecular studies (such as whole exome analysis) will be of considerable interest in our cohort of patients with dysautonomia.

At our institution, we have studied a large cohort of young patients (more than 400 children, adolescents, and young adults) with neurocardiogenic syncope and dysautonomia as documented by positive HUTT. We have also observed, as have other investigators\textsuperscript{1} in studies of this rather common disorder, that patients have multisystem complaints such as gastrointestinal motility disorders, distal paresthesias, heat intolerance with hyper- and hypohidrosis, in addition to sympathetic, and parasympathetic dysfunction. Furthermore, in our cohort, we have frequently observed Chiari malformations, raised intracranial CSF pressure, ligamentous laxity, brain disorders (cerebral dysgenesis) and epileptic states that cannot be explained by syncope from brain hypoperfusion. This constellation of clinical manifestations could be related to defective neural crest cell migration or dysfunction given the diffuse role of these neurodevelopmental processes in the formation of sympathetic and parasympathetic neurons of the autonomic nervous system, sensory neurons (dorsal root ganglia), enteric neurons, glia, connective tissue, osteocytes, and chondrocytes.\textsuperscript{21,22} The multiple roles of fibroblast growth factors in development of neural crest cells and their ultimate fates have been extensively studied by developmental neurobiologists.\textsuperscript{23} Thus molecular genetic studies of the multiple genes involved in neural crest cell migration and differentiation, particularly fibroblast growth factor genes, may be most informative in our understanding of the molecular basis for the phenotypic and multiple clinical manifestations in young patients with neurocardiogenic syncope and dysautonomia.

Limitations of this study include the retrospective collection and analysis of data in a small group of patients. Furthermore, only CSF metabolites of dopamine and serotonin were analyzed, although there is compelling evidence of severe norepinephrine and epinephrine defects in adult neurologic disorders of the autonomic nervous system. However, given our previous experience in studying disorders of biogenic amines in metabolic and genetic disorders of children and adolescents, we believe that demonstration of abnormal dopamine and serotonin...
metabolites in CSF in a significant proportion of youngsters with dysautonomia is an observation worthy of further study by modern molecular methods.

**Conflicts of Interest**

I. J. B., S. S. H., and J. L. have no conflicts of interest. M. N. is a consultant to Nonin Monitor (Minneapolis, Minn).

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