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Exaggerated Autonomic Asymmetry: A Clue to Nutrient Deficiency Dysautonomia

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Abstract

Seventeen adult Caucasian subjects were diagnosed clinically with dysautonomia, based on symptoms. Sixteen had asymmetrically different blood pressures measured simultaneously in both arms. Fourteen admitted to craving for sweets, salt or reactions to ingestion of sugar. Of these, 9 had abnormal erythrocyte transketolase changes indicating loss of thiamine homeostasis. Beriberi is the prototype for functional dysautonomia in its early stages. It is hypothesized that excessive ingestion of simple carbohydrates results in defective oxidative metabolism in autonomic nervous system control mechanisms, resulting in exaggeration of normal asymmetric reflex action, an effect similar to that induced by mild chronic hypoxia. Abnormal thiamine homeostasis and dysautonomia have been reported in a number of degenerative brain diseases.

Running title:

Nutrient deficiency dysautonomia with asymmetric brachial pulse pressures

Introduction

Dysautonomia is a broad term that describes any disease or malfunction of the autonomic nervous system. This includes postural orthostatic tachycardia syndrome (POTS), inappropriate sinus tachycardia (IST), vasovagal syncope, mitral valve prolapse dysautonomia, pure autonomic failure, neurocardiogenic syncope (NCS), neurally mediated hypotension (NMH), autonomic instability and a number of lesser-known disorders such as cerebral salt-wasting syndrome. Dysautonomia is associated with Lyme disease, primary biliary cirrhosis, multiple system atrophy (Shy-Drager syndrome) Ehlers-Danlos syndrome, and Marfan syndrome for reasons that are not fully understood (Köllensperger, M., et al. 2007). Quinn (Quinn, N., 1989) emphasized the diagnostic confusion surrounding a constellation of brain diseases where there is autonomic dysfunction in common and questioned how autonomic failure is defined, particularly in its milder form.

Blood pressure is usually performed on one arm only. Sixteen of seventeen patients with dysautonomia were found to have widely different blood pressures in the two arms when measured simultaneously by two operators. One patient was lost to follow up. Asymmetric action of the autonomic nervous system (ANS) is normal (Shannahof-Kalsa, D. S., 2007). Exaggeration of ANS reflexes may result from marginal oxidative dysfunction induced by thiamine deficiency (TD), other non caloric nutrients (Lonsdale, D.. 2009) or hypoxia, an example being partial hanging (paraphilia). (Ueno, Y., et al. 2003). Acute and chronic hypoxia induces sympathoadrenal responses (Johnson, T. S., et al. 1983) similar to those induced by TD (Voltmeyer, H. O., et al. 1993). Wernicke-Korsakoff syndrome, often associated with dysautonomia, is the most frequent manifestation of TD and other non caloric nutrient deficiencies in Western society (Kril, J. J., 1996) Dysautonomia is associated with a number of degenerative brain diseases (Quinn, N.,1989) and abnormal thiamine homeostasis (Gibson, G. E., Blass J P. 2007). Mitochondrial disruption from TD (Bettendorff L, et al. 1995) would curtail synthesis of thiamine triphosphate (TTP), an unknown factor in TD (Gandolf, M., et al. 2009).

Beriberi is the classic prototype for dysautonomia (Lonsdale, D., 2006). Death from Wernicke disease occurred in a woman receiving parenteral nutrition in spite of 24 mg of thiamine a day (Lonsdale, D., 1978). Increasing carbohydrate relative to total calories caused a decrease of plasma and urine concentrations of thiamine (Elmadfa, I., et al. 2001). Beriberi heart disease was reported in 23 Japanese patients, including 17 teenagers consuming soft drinks and carbohydrate foods (Kawai C, et al. 1980). TD is common in elderly patients (O'Keefe, H. O., et al. 1994)

Patients and Methods

The patient population consisted of 9 females and 8 males. Their ages ranged from 14 to 76 years, with an averaged of 44.2. Thirteen controls were healthy individuals consisting of 12 females and one male with an age range of 24 to 66 years and an average of 51.8 The symptoms of the 17 patients, all of which have been reported in dysautonomia (Lonsdale, D., 1987., 2009), are shown in Illustration 1. Illustration 1 -

attached

Erythrocyte transketolase activity and thiamine pyrophosphate effect were performed in all 17 patients (Massod, M. F., et al 1971). The study first measures the baseline activity of the enzyme (TKA) and the percentage acceleration over baseline after in vitro addition of thiamine pyrophosphate (TPPE)

Many of these patients had a lifelong history of polysymptomatic illness, one having begun at the age of 7 years after falling from a second floor window. Thirteen had either undiagnosed daily headaches or migraine. Thirteen experienced constant and/or recurrent alternating unilateral recumbent nasal congestion, indicating exaggeration of the normal ANS controlled nasal cycle (Shannahof-Kalsa, D. S., 2008). Two had received a proven diagnosis of sleep apnea, two with Lyme disease, one of whom had proven deficient esophageal peristalsis, two with mononucleosis and 3 women had a history of recurrent vaginal yeast infections. Four patients, one of whom had been found elsewhere to be homozygous for the MTHFR C677T mutation, had elevated blood homocysteine, (data not shown) one of whom had melanin pigmentation on both arms suggesting vitamin B 12 deficiency (Mori, K., et al. 2001. (Hoffman, C. F., et al. 2003). This individual, in whom the TPPE was repeatedly in the thiamine deficiency range, was addicted to sugar in any form, experiencing a severe reaction after consumption of blackstrap molasses taken as a “health food”. Sweet and/or salt craving was admitted in 14 of these patients and appeared to be an important etiologic component. One patient with a lifelong history of daily headaches, had a previous diagnosis of membranous glomerulo nephritis, myelodysplasia and esophageal ulceration. Echocardiography revealed mild tricuspid insufficiency. One male patient had a 20-year history of alternating urgency diarrhea and constipation, panic attacks and bipolar symptomology. One woman had experienced 12 PAP smears, each of which had been positive for HPV infection. One woman had a hysterectomy at age 38 years for endometriosis. Echocardiograms had shown mitral valve prolapse in one patient and mitral regurgitation without prolapse in another. A 38-year old man had mild aortic and tricuspid regurgitation and a 14-year old boy had an “insignificant patent foramen ovale”. A 38-year old man had migraine headaches and had passed 6 renal calculi. A man of 38 years of age presented with an 18 month history of chest pain, extreme fatigue and tinnitus Studies elsewhere had shown that he had Complex IV deficiency marked by repeatedly low blood levels of thiamine, even after the administration of 600 mg of a water soluble thiamine salt daily for an extended period.

Subject # 4 had been reported elsewhere to have elevations of anti-DNA and ASO titres. Subject # 9 had been found elsewhere to be infected with Blastocystis Hominis and Subjects # 1, 2 and 10 all had suffered recurrent yeast infections of the vagina. There are many instances of an association between organic disease and dysautonomia (Lonsdale, D., 2009). The blood pressures of 17 patients and 13 healthy individuals acting as controls are shown in Illustrations 2 and 3.

Illustrations 2 and 3 - attached

Results

Blood pressure asymmetry calculations were performed, using Chi square analysis. Each increase or decrease was assigned a value of 1. If the increase or decrease was the same value in both groups a value of 0.5 was assigned to each group. This calculation was done as a ratio and proportion statistic. Positives or negatives were squared and all became positive. The systolic, diastolic and pulse pressure increases or decreases were observed in the patient and control groups. indicating that the asymmetry was greater in the patients (Group 1) than in the controls (Group 2) (Illustration 4).

Illustration 4 - attached

One patient had a TKA that was below the laboratory norm. Ten, in some of whom there were multiple tests performed, had a TPPE of 18% or above, indicating thiamine deficiency or abnormal homeostasis Of the sixteen patients who had simultaneous blood pressures measured, there were 13 measurements of TKA in which the TPPE indicated abnormal thiamine homeostasis. The pulse pressures in these patients were compared with the 7 patients in whom the TPPE indicated thiamine sufficiency. The pulse pressures in those with abnormal TPPE were higher than those with acceptable TPPE (Illustration 5).

Illustration 5 -attached

Discussion

Asymmetry of the autonomic nervous system (ANS)

Asymmetry of the ANS is well known and three yogi techniques for selectively activating one half of the ANS are known (Shannahof-Kalsa, D. S., 2007). Simultaneously measured blood pressure asymmetry has not been reported to our knowledge. Other manifestations of asymmetry in these patients appear to be exaggeration of otherwise normal reflex activity.

Autonomic asymmetry has been demonstrated in migraineurs (Aynon, Y., et al. 2004). The frontal and temporal lobes have a division of responsibility in regulation of heart rate and blood pressure (Foster, P. S., et al. 2006). Midbrain activity, resulting in right-left asymmetry in sympathetic drive, predisposes to cardiac arrhythmia (Critchley, H. D., et al. 2005). Asymmetric innervation of the ureter and fallopian tubes has been demonstrated (Lychkova, A. E., 2005). Autonomic nose innervation is asymmetrical and oscillates in a regular nasal cycle. The authors concluded that hypothalamic instability results in marked autonomic asymmetry (Eccles, R., Eccles, K. S., 1981). Dysfunctional esophageal peristalsis in one of the patients indicated failure of parasympathetic drive, since the esophagus lacks sympathetic innervation. Reduced parasympathetic activity in autism has been published (Ming, X., et al 2005).

Whether the asymmetric blood pressures in these patients are exaggeration of normal ANS asymmetry, anatomical difference in the origin of the right brachial artery from that of the left, heart valve deficiencies as revealed in some of our patients, or a combination of these variables is unknown. Pulse pressures are known to be wide in thiamine deficient beriberi (Inouye, K., Katsura, E., 1965) Dysautonomia

Familial Dysautonomia (Riley-Day syndrome) has many symptoms (Lonsdale, D., 1987, 1990). A case report of a woman with asymmetric functional dysautonomia revealed that the pulse pressures reduced with dietary correction and nutrient supplements that included thiamine and magnesium (Lonsdale, D., 1990). Combination of hypertension and orthostatic hypotension (OT) in older individuals (Lee, T., et al. 2005) was found in 13.4% of hypertensive and 5.5% normotensive subjects (Fedorowski, A., et al. 2009). If asymmetric blood pressures are relatively common, it may depend on which arm is used for diagnostic purposes.

Neural reflexes regulate immunity, involving the nicotinic acetylcholine receptor that inhibits innate immune responses (Rosas-Ballina, M., Tracey, K. J., 2009). Failure might create a greater susceptibility to opportunist infection as in several of our patients. It has been hypothesized that dysfunctional oxidative metabolism provides the underlying etiology for dysautonomia and its association with a number of diseases. (Lonsdale, D., 2009).

Bruxism, common in sleep, was reported in the awake state in multiple system atrophy (MSA) (Wali, G. M., 2004). McKeon and associates found that one per cent of 15,000 patients evaluated for paraneoplastic neurological autoimmunity were seropositive for the nicotinic ganglionic acetylcholine receptor autoantibody (alpha3-AChR), many of whom had dysautonomia (McKeon, A., et al. 2009). One of our patients had a diagnosis of Sjogren syndrome, reported in dysautonomia due to acetylcholine receptor antibodies (Bourcier, M. E., Vanik, A. L., 2008). She had also been diagnosed with Lyme disease, itself associated with Holmes-Adie syndrome (Stricker, R. B., Winger, E. E., 2001).. Two of our patients had a history of undiagnosed daily headaches, sometimes associated with autonomic dysfunction (Montagna, P., 2006).

Oxidative Dysfunction

Evidently asymmetry can become symptomatic, as in alternating recumbent nasal congestion and exaggerated asymmetric blood pressures. Chronic hypoxia in the rat stimulated sympathoadrenal system functions, dependent on the degree and duration of hypoxic exposure (Johnson, T. S., et al. 1983).

Thiamine Homeostasis

Altered thiamine homeostasis in many neurodegenerative diseases (Gibson, G. E., Blass, J. P., 2007) and defective acetyl choline metabolism (Barclay, L. L., et al. 1981), represents a model system for exploring the pathological mechanisms (Hazell, A. S., Butterworth, R. F., 2009).

Ten of our patients had a TPPE over 18%, indicating abnormal thiamine homeostasis. Some had repeated TPPE (Illustration 5) in or out of range. In only two patients was a zero TPPE recorded, indicating full TPP enzyme saturation. A marginal TPPE, (1-18%) may represent a graded transition from cofactor sufficiency to deficiency symptoms.

TD in mice reduced transketolase activity in cortex and hippocampus, without significantly affecting thiamine dependent enzymes. Pentose-phosphate dysfunction, a pathway dependent on transketolase, contributed to impaired hippocampal neurogenesis (Zhao, Y., et al. 2009), Magnetic resonance mapping in TD rats demonstrated no lesions in the frontal cortex in the early stages of deficiency (Dror, V., et al. 2009). Striking preservation of intellect, with severe motor disability was noted in MSA (Quinn, N., 1989), suggesting that any form of relatively mild oxidative dysfunction particularly affects the lower brain. Peters, who did the early classic experiments with thiamine after its synthesis, noted that no certain difference between the respiration of normal and thiamine deficient pigeon's brain had been observed. "With glucose present, there was no doubt that the respiration was lowered and, as in the case of the lactate accumulation, especially in the lower parts of the brain" (Peters, R. A., 1936). Panic attacks in 15 patients suggested fragmented fight-or-flight reflexes as occurred after CO2 inhalation (Blechert, J., et al.

2010). One of our patients, a woman of 38 years, began her symptoms at the age of 7 years after a fall from a second floor window. Physical stress can initiate intermittent symptoms in a marginal metabolic state (Lonsdale, D., 2009).

Twenty adolescent patients with abnormal erythrocyte transketolase were treated successfully by nutritional correction (Lonsdale, D., Shamberger, R. J.,1980), suggesting that our 17 patients may represent these adolescents in their later years. Although treated by appropriate nutritional counseling and supplements that included thiamine tetrahydrofurfuryl disulfide, results have been variable as in thiamin treatment of other neurological diseases (Gibson, G. E., Blass, J. P., 2007).

Brain thiamine deficiency

Brain TD mechanisms have remained elusive. TTP is known to have some connection with the function of chloride channels (Bettendorff, L., et al. 1994) and has long been known to be important in brain metabolism (Pincus, J. H., et al. 1973.Cooper, J. R., Pincus, J. H., 1979). It is synthesized in rat brain mitochondria from TPP, using energy for the reaction coupled to the respiratory chain (Gangolf, M., et al. 2009) but its role is unclear. Deficiency might occur from mitochondrial disruption. It is twice more abundant in brainstem than in cortex or cerebellum (Gangolf, M., et al. 2010) and is in high concentration in the electric organ of the Electrophorus electricus and Torpedo marmorata (Bettendorff, L., et al. 1987). The electric organ is an adaptation of a neuromuscular junction. The potential actions of TTP may be similar to ATP, recently found to be an extracellular messenger (Khakh, S., Burnstock, G., 2009).

Thiamine may be involved in acetylcholine release (Eder, L., et al. 1976) and its synthesis is dependent on adequate action of the citric acid cycle and acetyl CoA. Mitochondria are uncoupled and their cristae disorganized with experimental TD. Respiratory control and morphology are restored with thiamine (Bettendorff, L., et al. 1995).

Conclusion and Hypothesis

The symptoms in our patients are often considered to be psychiatric or psychosomatic. A biochemical classification for disease has been proposed (Quinn, N., 1989). Dysautonomia may be the connecting link to organic disease through loss of efficiency in oxidative metabolism, the central control mechanisms being affected first (Lonsdale, D., 2009). We hypothesize that mild to moderate hypoxia and/or thiamine deficiency both give rise to exaggeration of centrally controlled mechanisms involved in all survival reflexes, mediated normally through a balanced reaction of the ANS and endocrine system. The sympathoadrenal system is evolutionally designed for short term action when energy is consumed at an accelerated rate, as in fight-or-flight. Automatically initiated, it is our response to stress, the nature of which has changed radically from the situations encountered by our ancestors. That, together with dietary excesses, particularly in the universal ingestion of sugar, appears to be responsible for initiating long term disease related to the synthesis and use of cellular energy. Failure of ANS cholinergic neurotransmission might follow from TD and/or other cofactors involved in glucose metabolism, exposing the organism to adrenal medullary release of epinephrine.

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Illustrations

Illustration 1

Symptoms recorded from 17 patients with a clinical diagnosis of dysautonomia

Sleep problems/insomnia/bruxism/night cough/eating/sleep apnea	**17**
Fatigue	**15**
Emotional lability/depression/panic attacks	**15**
Joint, muscle or limb pain/muscle weakness	**15**
Sugar or salt craving/reaction to ingestion of sugar	**14**
Gastritis/ gastro esophageal reflux/abdominal pain or discomfort/dysphagia	**13**
Daily headaches or migraine	**13**
Nasal congestion, with or without alternating recumbent congestion	**13**
Feeling of suffocation, “air hunger”/ dyspnea at rest	**13**
Numbness/parasthesiae/cold extremities	**13**
Heart palpitations/undiagnosed recurrent chest pain	**11**
Dizziness/vertigo/feeling of instability	**11**
Constipation/diarrhea/encopresis/bowel urgency/mega stools	**10**
Memory loss	**9**
Appetite changes from voracious to anorexic	**9**
Urinary frequency/urgency/frequent nocturia	**9**
Intolerance to ambient temperature and/or changes in barometric pressure	**9**
Nausea and/or vomiting	**8**
Coughing and/or sneezing spasms/chronic cough/ hoarseness	**7**
Weight gain of more than twenty pounds	**5**
Premenstrual syndrome in 8 premenopausal women	**5**
Tremor	**5**
Tinnitus/ history of mononucleosis or Lyme disease	**3 of each**
Impotence/an- or hyper-hydrosis/chemical sensitivity	**2 of each**

Illustration 2

Blood pressures in both arms measured simultaneously in 17 patients with dysautonomia

	BLOOD PRESSURES					
	Right Arm			Left Arm		
Subject	SP	DP	PP	SP	DP	PP
1	160	82	78	150	80	70
	140	88	52	150	82	68
	130	76	54	114	76	38
2	110	70	40	130	86	44
3	120	82	38	166	90	76
	154	84	70	146	80	66
	122	68	54	140	70	70
	130	72	58	140	70	70
5	120	90	30	144	98	60
6	108	70	38	132	78	54
7	150	90	60	158	98	60
8	150	70	80	192	78	114
	170	74	96	180	80	100
9	160	70	90	170	70	100
10	130	104	26	156	110	45
11	110	80	30	120	86	34
12	130	74	56	116	84	32
13	136	90	46	120	74	46
14	114	90	24	98	68	30
	114	66	48	100	75	25
	100	60	40	100	75	25
15	146	100	46	160	100	60
16	102	82	20	127	82	45
	104	76	28	121	80	41
	104	80	24	127	80	47

Illustration 3

Blood pressures measured simultaneously in both arms in 13 healthy adults

	RIGHT ARM		PULSE P	LEFT ARM		PULSE P
Age	Systolic	Diastolic		Systolic	Diastolic	
52	100	74	26	112	76	36
43	134	84	50	120	76	44
57	120	70	50	104	70	34
24	98	60	38	98	66	32
66	110	66	44	108	76	32
30	126	96	30	128	90	38
58	146	86	60	130	80	50
58	140	76	64	150	76	74
62	142	88	54	146	86	60
63	150	92	58	152	88	64
59	148	92	56	150	98	52
45	128	78	50	120	76	44
57	134	90	`44	138	86	52
Mean	128.9	80.9	44.6	127.4	80.3	47.1

Blood pressures recorded simultaneously in both arm of 13 healthy controls

Illustration 4

Chi square analysis showing the increased blood pressures in 16 patients compared with those in 13 healthy adults.

Illustration 4

Group 1	+	-	Group 2	+	-	Chi Sq	P
Systolic	**7.5**	**18.5**		**5.5**	**7.5**	**7.26**	**<0.01**
Diastolic	**8.5**	**17.5**		**8.0**	**5.0**	**6.27**	**<0.02**
Pulse P	**6.5**	**198.5**		**7.0**	**6.0**	**8.80**	**<0.01**

Illustration 5

Results of t-test on pulse pressures in 13 patients with high TPPE vs 7 with normal TPPE (R, right: L, left) 13 RPP vs 7 RPP P

	Subjects with increased TPPE			
Subject	TKA	TPPE	RPP	LPP
1	51	20	78	70
1			52	68
1			54	38
3	42-64	29-2	38	76
3			70	66
3			54	70
3			58	70
4	43-64	29-13		
7	42-62	31-15	60	60
8	62-76	26-17	80	114
8				
9	53	32	90	100
12	73	25	45	46
13	43	21	45	46
15	37-80	38-0	46	60
16	48	27	20	45
		Mean	56.4	66.3
	Subjects with normal TPPE			
2	45	4	40	44
5	63	8	30	60
6	56	9	38	54
10	47-75	14-0	26	45
11	72	14	30	34
14	81	4	24	30

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