

Report & Analysis

Your Question

In the Summer of 1998 I experienced spells of fatigue, temperature intolerance & dizziness. I was also going through a lot of stress in my life at the time.

My major symptom of concern was an accelerated heartbeat of 160-180.

The cardiologist diagnosed my illness as dysautonomia, and noted that there was also considerable fluctuation in my blood pressure.

The 1st prescription I was given was a beta blocker: Atenolol (20mg per day), which I am still taking today. When I still complained of continuing dizziness after I began to take Atenolol, the doctor also prescribed Proamatin, 30mg per day.

For the past year now I have cut the dose of Proamatin from 30 to 10 mg daily, and at the same time have increased my exercise regime significantly. I haven't noticed any difference in my physical feeling connected with the reduction of the Proamatin, but about 1 hour after taking the 10 mg pill, however, I get uncomfortable "goose bumps" on my skin, which with time disappear.

- 1.) Is there a significant risk involved for my health if I stop using the Proamatin altogether?
- 2.) Is there any other drug I could substitute for it?
- 3.) Are there any long term risks/benefits in continuing taking Proamatin?

Report

Lay Summary

Dysautonomia is a disease of the nerves that control your bodily function. Its cause is unknown at present and a familiar form of the disease is known to be caused by problems in the genes. The treatment is to control the symptoms. Proamatine is a relatively new drug and frequently used to treat orthostatic hypotension (low blood pressure when standing up). It has been used to manage the blood pressure in dysautonomia. However, it has a number of side effects including "goose bumps" on the skin (for other side effects see content). If the goosebumps persist or causes severe discomfort, you should tell your doctor and may consider changing to other drugs. As Proamatine is just to control the symptom but not to cure the disease, there are a number of medications that can be used in addition to or in place of Proamatine (for details see content). You should be careful about the side effects and a number of problems associated with Proamatine. As the gene defect of familiar dysautonomia has been discovered recently, gene therapy may become available for treatment in the future. Alternatively, a couple of research reports have appeared suggesting that acupuncture therapy may benefit this or similar conditions (for details see content).

Detailed Information

What is "Dysautonomia"

The autonomic nervous system is the "automatic" or "unconscious" nervous system. It controls and regulates virtually all of our body functions and systems, such as blood pressure, pulse, body temperature, breathing, sweating, bowel function and sleep patterns. The autonomic nervous system is made up of two parts: the sympathetic nervous system tends to increase and accelerate or speed up body functions, the parasympathetic nervous system tends to slow down, relax, and put the breaks on body functions. In a normal situation, the two divisions of the autonomic nervous system work together to control these functions in a continuous manner reacting normally to stimulus.

When the autonomic nervous system becomes "out of balance," it is similar to a car that needs a tune-up. When this occurs, these body functions may either speed up or slow down at inappropriate times with a very noticeable effect on the person. This may occur for no apparent reason. You may be sitting quietly at home reading or watching television, driving down the highway or shopping for groceries in a store. The autonomic nervous system suddenly decides to send out a burst of signals to speed up all body processes. When this occurs the symptoms may be extremely severe and frightening. This faulty regulation of the autonomic system is referred to as "dysautonomia." The exact reason for some people to develop this problem is not clear presently and it is most likely related to problems in the genes. Dysautonomia may also occur as a response to stress whether it be emotional or physical. Such things as a severe illness, job stress, family problems, buying or building a house, a move cross country, going off to college, having a child and similar type occurrences in our life may trigger the autonomic system to react

inappropriately. While these symptoms are extremely frightening, frustrating and uncomfortable, it is not life threatening. However, if left untreated, it may become lifestyle threatening.

Most patients who suffer from mitral valve prolapse syndrome will have dysautonomia as the cause of their symptoms. It is likely that mitral valve prolapse is not the cause of what is going on but the autonomic imbalance or dysautonomia is the actual cause. Why these two things occur together is not entirely clear. IN some cases it is also related to faulty regulation of the body's fluid balance. In other words, patients with this condition generally have a lower than normal blood volume or amount of fluid that circulates through the arteries and veins of the body. This may result in symptoms of dizziness, lightheadedness and low blood pressure. Many times the blood pressure will drop upon standing or arising suddenly from a seated position.

In order to treat the symptoms of this condition it is necessary to understand the autonomic nervous system and why it is working improperly and take appropriate steps to correct these abnormalities.

Things that tend to aggravate dysautonomia include: medications such as over the counter sinus and cold medications, caffeine (whether it be coffee, tea, chocolate, etc.), anything that drops blood volume (such as becoming anemic or sudden blood loss, and other stresses such as illnesses. We also know that at times becoming deconditioned can lead to dysautonomia. Prolonged bed rest following surgery, breaking a leg or something similar can cause dysautonomia. The astronauts who participate in prolonged space shuttle missions tend to exhibit symptoms and physical findings of dysautonomia. Some of the findings and treatment for this condition have been the result of recent research done in connection with the space program

[About Familial Dysautonomia](#)

There is a form of dysautonomia that is inheritable and caused by problems of the genes. It is called familial dysautonomia, also known as Riley-Day Syndrome (After the two pediatricians that described the disorder in 1949) and HSAN III (hereditary sensory and autonomic neuropathy, type III)

Although the public and many medical professionals are unaware of familial dysautonomia, a striking 1 in 30 Ashkenazi Jews are carriers of the more common FD mutation, a prevalence similar to the better known disorder, Tay-Sachs disease. With the identification of the two mutations that cause FD in January, 2001, carrier screening for these mutations are now available. For more information on the identification of the gene responsible for FD and on how you can be tested to see if you are a carrier these mutations, go to [What's New at FD Village](#).

Familial dysautonomia (FD) is an autosomal recessive genetic disorder that affects the autonomic and sensory nervous systems. FD is seen in males and females equally, among

Ashkenazi (Eastern European) Jews. Some common features of FD include: the lack of overflow tears while crying; a decreased ability to feel pain or temperature sensations; inappropriate blood pressure and body temperature fluctuations; trouble with feeding, swallowing and gastrointestinal motility; hypotonia; developmental delays; recurrent pneumonias (from aspiration); scoliosis and kyphosis; increased sweating; transient skin blotching; and decreased stature.

Presently, there is no cure for this progressive disorder and treatment is aimed at controlling symptoms and avoiding complications. Survival is increased with treatment, and new research will hopefully continue towards a cure in time to save the lives of the brave children and adults who suffer from familial dysautonomia.

Increased awareness and research in familial dysautonomia will help develop more treatment options and ultimately find a cure. Further insight into FD will also provide help for related sensory and autonomic nervous systems disorders and other commonly seen medical conditions. The medical and scientific community will develop a better understanding of how the body regulates functions such as blood pressure (both hypertension and orthostatic hypotension are seen in FD), pain, body temperature, corneal wound healing, swallowing, reflux and gastrointestinal motility, and nervous system cell death (apoptosis).

[Familial dysautonomia has been found to be caused by mutations in the IKBKAP gene.](#)

Features are lack of tearing, emotional lability, paroxysmal hypertension, increased sweating, cold hands and feet, corneal anesthesia, erythematous blotching of the skin, and drooling. Absence of the fungiform papillae of the tongue is characteristic, and scoliosis is often severe. Neuropathic joints of the Charcot type also develop (Brunt and McKusick, 1970). Yatsu and Zussman (1964) provided follow-up on 1 of the 5 cases reported by Riley et al. (1949). The patient died suddenly at age 31. In the United States, it is a disorder almost completely limited to persons of Ashkenazi Jewish extraction (Brunt and McKusick, 1970). In Israel, as in the United States, most cases were Ashkenazim from Poland, according to Goldstein-Nieviazhski and Wallis (1966). Maayan et al. (1987) calculated an incidence of 1 in 3,703 for familial dysautonomia among Ashkenazi Jews in Israel. Rare non-Jewish cases of presumed familial dysautonomia have been reported (e.g., Burke, 1966), but the diagnosis is usually in question. For example, the patient of Burke (1966) has been seen by Rogers (1993) who concluded that although she has a hereditary sensory neuropathy, the disorder is not familial dysautonomia.

Axelrod and Abularrage (1982) reported on survival in dysautonomia. From 1969 to 1982, 227 patients had been referred to the Dysautonomia Center at New York University. At the time of report, 59 patients were 20 years of age or older and accounted for 33% of the living patients. The oldest was 38 years old. Axelrod (1998) provided an update of the patients at the Dysautonomia Center. In 1998, 40% of the active population of 307 patients were over the age of 20 years. In addition to worsening peripheral sensory dysfunction, the adults complained of poor balance, unsteady gait, and difficulty concentrating. They were prone to depression, anxieties, and even phobias.

Sympathovagal balance became more precarious with worsening of orthostatic hypotension, development of supine hypertension, and even occasional bradyarrhythmias.

Gadoth et al. (1983) found a prolonged pupil cycle time (light response) and interpreted it as indicative of denervation hypersensitivity. The denervation may be functional rather than structural; parenterally administered Mecholyl causes overflow tearing and temporary normalization of deep tendon reflexes and response to intradermal histamine. Fishbein and Grossman (1986) described the pulmonary complications in a 29-year-old man with familial dysautonomia. In 2 Jewish sibs with this disease, Brown et al. (1964) described the autopsy findings, namely, demyelination in the medulla, pontine reticular formation and dorsolongitudinal tracts, and degeneration, pigmentation and loss of cells in autonomic ganglia.

Goodall et al. (1971) demonstrated a decrease in synthesis of noradrenaline. Weinshilboum and Axelrod (1971) found decreased dopamine-beta-hydroxylase (DBH), the enzyme that converts dopamine to norepinephrine. Some dysautonomic children had no plasma DBH activity and their mothers had decreased activity. Siggers et al. (1976) measured the 3 nerve growth factor (NGF) subunits and found a 3-fold increase in serum antigen of the beta unit with normal function measurements. This suggested a qualitative abnormality of beta-NGF in the disorder. Abnormality of NGF had been reported in neurofibromatosis and in medullary carcinoma of the thyroid. In cultured fibroblasts from dysautonomic patients, Schwartz and Breakefield (1980) found that by bioassay nerve growth factor was about 10% as active per ng of immunoreactive protein as that from controls. The beta-adrenergic agonist isoproterenol produced no change in immunoreactive beta-NGF in dysautonomia whereas a marked increase occurred in control cells. The level of beta-NGF by immunoassay was the same in dysautonomia and control cells in the unstimulated state. A defect in the processing of precursor or in the structure of biologically active beta subunit of NGF was postulated. Johnson et al. (1980) showed that in rats and guinea pigs dorsal root ganglion neurons are destroyed by exposure in utero to maternal antibody to NGF. They suggested this as a useful experimental model for familial dysautonomia. The use of the 'candidate gene' approach in an attempt to determine the 'cause' of a specific disorder was illustrated by the work of Breakefield et al. (1984). Using a cloned genomic probe for human beta-nerve growth factor, they identified RFLPs in the beta-NGF gene and in 4 informative families with 2 children with familial dysautonomia found 'no consistent co-inheritance of specific alleles with the disease.' Thus, they appear to have excluded a defect in or near the structural gene for beta-NGF as the cause of familial dysautonomia. By means of RFLPs related to nerve growth factor receptor, Ozelius et al. (1986) excluded this gene as the site of the mutation in familial dysautonomia; the study included 7 dysautonomia families with multiple affected members. See Breakefield et al. (1986). Pearson et al. (1982) reported anatomically discrete depletion of substance P immunoreactivity in the substantia gelatinosa of spinal cord and medulla of patients with familial dysautonomia. Substance P, an undecapeptide, is thought to be involved in transmission of nociceptive information at synapses of primary sensory neurons.

Conditions that have been confused with dysautonomia include Biemond congenital and familial analgesia and congenital sensory neuropathy with anhidrosis. Consistent neuropathologic findings in the sural nerve (Pearson et al., 1975) may be the best diagnostic criterion to differentiate familial dysautonomia from other forms of congenital sensory neuropathy (Axelrod et al., 1983). The clinical diagnosis is based on the presence of 5 signs: lack of axon flare after intradermal injection of histamine, absence of fungiform papillae on the tongue, miosis of the pupil after conjunctival instillation of methacholine chloride (2.5%), absent deep tendon reflexes, and diminished tear flow. Axelrod et al. (1983) reported the case of a gypsy child with congenital sensory neuropathy who had all 5 signs in addition to skeletal abnormalities, dysmorphic features, and hypohidrosis. The sural nerve biopsy was inconsistent with dysautonomia, however. Many non-Jewish cases of 'familial dysautonomia' may be another form of congenital sensory neuropathy.

Axelrod et al. (1987) suggested that the possibility of familial dysautonomia should be suspected in a child of Eastern European Jewish extraction with breech delivery, meconium staining, poor suck, hypotonia, or hypothermia. The diagnosis could be confirmed by inspection of the tongue for fungiform papillae, determination of deep tendon reflexes, and performance of intradermal histamine and intraocular pilocarpine tests. If results in either of the latter 2 tests are normal or equivocal, they should be repeated after 6 weeks of age.

Blumenfeld et al. (1993) assigned the gene for familial dysautonomia to chromosome 9 by family linkage studies using DNA markers. The defined DNA markers, useful for genetic diagnosis, localized the gene to 9q31-q33. A maximum lod score of 21.1 with no recombinants was achieved with D9S58. This marker also showed strong linkage disequilibrium with DYS, with one allele present on 73% of affected chromosomes compared to 5.4% of controls. D9S53 and D9S105 represented the closest flanking markers.

Eng et al. (1995) used CA-repeat polymorphisms located in the 9q31-q33 region for prenatal diagnosis of familial dysautonomia by the linkage principle. All 7 families studied were informative for the markers and fetal diagnoses were made in 8 pregnancies. Six fetal diagnoses were predicted with more than 98% accuracy, while 2 with recombinations were predicted with at least 88% and 92% accuracy.

Using linkage and linkage disequilibrium analyses with highly polymorphic dinucleotide repeat markers known to flank the familial dysautonomia locus, Oddoux et al. (1995) performed prenatal diagnosis in 8 pregnancies in 7 informative families. All of the fetuses were predicted to be heterozygous unaffected; 7 had come to term and were normal.

Using 11 new polymorphic markers, Blumenfeld et al. (1999) narrowed the location of DYS to less than 0.5 cM, between 2 specific markers. Two markers within this interval showed no recombination with the disorder. Haplotype analysis confirmed this candidate region and revealed a major haplotype shared by 435 of 441 FD chromosomes, indicating a striking founder effect. Three other haplotypes, found on the remaining 6 FD

chromosomes, might represent independent mutations. The frequency of the major FD haplotype in the Ashkenazim (5 in 324 control chromosomes) was consistent with the estimated DYS carrier frequency of 1 in 32, and none of the 4 haplotypes associated with FD was observed on 492 non-FD chromosomes from obligatory carriers. The haplotype information made it possible to provide accurate genetic testing both for families with FD and for carriers, on the basis of close flanking markers and the capacity to identify more than 98% of FD chromosomes by their haplotype.

Slaugenhaupt et al. (2001) and Anderson et al. (2001) demonstrated that the major haplotype of familial dysautonomia is associated with a mutation that affects the donor splice site of intron 20 of the IKBKAP gene. A minor haplotype was found to be associated with a missense mutation that was predicted to disrupt a phosphorylation site.

HISTORY OF DYSAUTONOMIA RESEARCH

Axelrod (1998) provided a historical perspective on familial dysautonomia, highlighting the early contributions of Dancis. Recognition of this disorder, first described by Riley et al. (1949), spans almost 50 years. To Riley's finding of consistently diminished tear production, Dancis and Smith added 2 other consistently abnormal tests: lack of an axon flare (Smith and Dancis, 1963) after intradermal histamine and absence of fungiform papillae on the tongue (Smith et al., 1965). The other 2 particularly helpful diagnostic features, Ashkenazi-Jewish heritage and decreased deep tendon reflexes, were also defined.

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Familial Dysautonomia Description

Familial dysautonomia [FD] is one example of a group of disorders known as hereditary sensory and autonomic neuropathies [HSAN]. All HSAN are characterized by widespread sensory dysfunction and variable autonomic dysfunction caused by incomplete development of sensory and autonomic neurons. The disorders are believed to be genetically distinct from each other. Unlike the other HSAN, FD has been noted only in individuals of Ashkenazi Jewish extraction and so it is included as one of the Jewish

genetic diseases.

Individuals affected with FD are incapable of producing overflow tears with emotional crying. Frequent manifestations of FD include inappropriate perception of heat, pain, and taste, as well as, labile blood pressures and gastrointestinal dysmotility. Other problems experienced by individuals with FD include excessive sweating, dysphagia and vomiting, aspiration and frequent pneumonia, speech and motor incoordination, labile blood pressures (episodic hypertension and postural hypotension), poor growth and scoliosis. Yet affected individuals usually are of normal intelligence. FD patients can be expected to function independently if treatment is begun early and major disabilities avoided.

FD Clinical Symptoms

The most distinctive clinical feature is absence of overflow tears with emotional crying although it can be normal for a child not to have tearing until 7 months of age. Other signs of the disorder can be present from birth such as a high prevalence of breech presentation, weak or absent suck and poor tone.

Difficulty feeding is observed in 60% of infants in the neonatal period. Poor suck and misdirected swallows often persist and put the patient at risk for aspiration pneumonia, the major cause of lung infections. If gastroesophageal reflux is present, the risk for aspiration increases.

Approximately 40% of patients will react to stress (infection or emotional events) with a constellation of symptoms termed the dysautonomia crisis. In addition to vomiting, there is frequently increased heart rate and blood pressure, sweating, and a negative change in personality.

Further supportive evidence is provided by findings of decreased response to pain and temperature, orthostatic hypotension, red blotching of the skin, and increased sweating. Other frequent signs are :

- delayed developmental milestones
- speech and motor incoordination
- unsteady gait
- labile blood pressure
- corneal anesthesia
- marked sweating with excitement, eating or the first stage of sleep
- breath-holding episodes
- poor growth
- spinal curvature (in 90% by age 13 yrs)
- red puffy hands

Diagnosis of FD

FD should be suspected when the an individual has one or more of the symptoms listed above. However a clinical diagnosis is supported by the following constellation of clinical signs:

- Parents of Ashkenazi Jewish background
- Absence of fungiform papillae on the tongue [Compare NORMAL and FD tongue images].
- Decreased deep tendon reflexes
- Lack of an axon flare following intradermal histamine.[Compare HISTAMINE TESTS- Normal and FD responses]
- No overflow tears with emotional crying

For a firm diagnosis, an effective individual should have mutations in the IKBKAP gene. Over 99% will have two mutations in this gene.

FD Genetics and Genetic Testing

Familial Dysautonomia is a genetic condition that occurs almost exclusively among people of Eastern European (Ashkenazi) Jewish descent. In this population it is estimated that one in 30 individuals are carriers of the FD gene.

FD is transmitted in a recessive gene fashion.

- For a child to be affected, he or she must inherit two copies of the FD gene
- All parents of children with FD are carriers of the recessive gene that transmits the disease.
- A parent or carrier has no symptoms or warning signs of being a carrier of the FD gene.
- If two carriers have a child, there is a 25% chance with each pregnancy that the recessive genes will pair and result in a child being affected with FD.

In 1993 the FD gene was localized to the long arm of chromosome 9 (9q31) and flanking genetic markers (benign variants of DNA) were available. This information made possible prenatal diagnosis and carrier genetic testing for people with a family history of FD or whose spouses had a history.

As of Spring 2001

General population screening will be available.
Testing of individuals without a family history will be available.

The FD gene has been identified as IKBKAP. Two mutations in this gene can cause FD.

- The most common mutation is in intron 20; >99% of FD individuals are homozygous for this mutation that is tissue specific and results in skipping of exon 20 only in brain mRNA. Thus, the gene product IKAP is not expressed in brain but is expressed in lymphoblasts.
- The second mutation is a missense mutation on exon 19 (G to C change). This may result in disrupting a phosphorylation site on IKAP and decreasing its effectiveness.

How is testing performed?

Genetic testing is performed on a small sample of blood from the interested individual. The DNA is examined with a special probe designed to detect the two known specific mutations. The reliability of the test is greater than 99%

Who should be tested?

- Any individual with Ashkenazi Jewish (Eastern European) origin has a 1 in 30 risk of being a carrier and should consider screening
- Any individual who has a family history of FD has an increased risk of being a carrier and should consider a screening test.
- If your partner is a carrier, then you should be tested

To do prenatal diagnosis:

If both members of a couple are shown to be carriers by genetic testing, prenatal diagnosis by amniocentesis (14-17 weeks) or chorionic villus sampling (10-11 weeks) is possible.

Where is testing performed?

These genetic tests are currently performed only at laboratories that have been designated by the Dysautonomia Foundation. These laboratories, at NYU and Mount Sinai in New York and at Haddassah Medical Center in Jerusalem, have demonstrated their ability to perform these tests with a high-degree of reliability.

Testing is performed only after the interested person has received genetic counseling to clarify the benefits and limitations. The Dysautonomia Foundation's designated genetic counseling center is at NYU School of Medicine. Israelis may receive genetic counseling at Haddassah Medical Center.

Genetic tests are performed only with an individual's consent. Other genetic tests will not be performed in the absence of consent. However, from a single blood sample it is possible to test for other conditions that also affect Ashkenazi Jewish children. These include Tay-Sachs disease, Canavan disease, cystic fibrosis, Gaucher disease, Bloom syndrome, Fanconi anemia A, and Niemann-Pick disease.

Additional information is available at

Human Genetics Program
NYU School of Medicine
550 First Avenue, MSB 136
New York, NY 10016
tel: 212 263-5746
fax: 212 263-7590
email: elsa.reich@med.nyu.edu

FD Prevention and Therapy

Although the FD gene has been identified and it seems to have tissue specific expression at present, there is no definitive treatment. Thus treatment remains preventative, symptomatic and supportive. Although penetrance is complete, there is marked variability in expression of the disease. Thus problems can vary considerably among patients and with different ages. Thus it is recommended that patients avail themselves of the specialized resources to obtain individualized treatment plans. Some of the more commonly needed treatments are as follows:

- artificial tears
 - special feeding techniques
 - special therapies (feeding, occupational, physical, speech)
 - special drug management of autonomic manifestations
 - respiratory care
 - protecting the child from injury (coping with decreased taste, temperature and pain perception)
 - treatment of orthopedic problems (tibial torsion and spinal curvature)
 - compensating for labile blood pressures
-

FD Services Available

Dysautonomia Treatment and Evaluation Center

The Dysautonomia Treatment and Evaluation Center is under the direction of Dr. Felicia B. Axelrod. The Center was established at NYU Medical Center in 1969 to provide care to individuals affected with the genetic disorder familial dysautonomia (FD). This is the only Center for FD in the United States and thus serves as a resource for patients and physicians worldwide in assessing and treating FD. In addition, expertise has been developed in assessment of other pediatric disorders with autonomic dysfunction and other congenital sensory neuropathies. At the initial evaluation, the patient receives a comprehensive examination. When indicated, tests are performed to confirm diagnosis,

assess current status and provide information for the development of a personalized treatment plan. A thorough report with impressions and recommendations is sent to the referring physician and other health care providers as requested by the parents. If a diagnosis of FD is confirmed, then patients are seen annually to modify treatment programs as indicated. For patients who do not have FD and who require more extensive evaluation of the autonomic and sensory systems, more extended cardiovascular studies may be performed such as tilt testing, heart rate variability with Holter monitoring, signal-averaged electrocardiogram. Clinical observations and laboratory data are continually recorded at the Dysautonomia Treatment and Evaluation Center so that a data bank of information is being accumulated. This aids in periodic review and analysis of dysautonomia data to determine incidence of particular problems, effectiveness of therapy and long term sequelae of the disorder as well as of treatment programs while maintaining patient confidentiality. In addition, patients may be given the opportunity to participate in clinical studies. Currently research in FD includes developing better treatment of orthostatic hypotension which includes trials of Florinef and a new alpha agonist, midodrine; better control of centrally induced nausea and vomiting with diazepam and Catapres; and consideration of the possible role of neuronal trophic factors. Finally, as the gene for FD has been recently identified as IKBKAP (March 2001), it is anticipated that the Center will eventually launch more treatment trials and possibly gene therapy.

Patients are seen either by physician referral or by direct request. Appointments are scheduled by calling the Center:

Telephone (212) 263-7225 Fax (212) 263-7041
E Mail Felicia.Axelrod@med.nyu.edu

About ProAmatine

Midodrine (MI-doe-dreen), sold in the US as the brand name "ProAmatine", is a drug used to treat orthostatic hypotension (decreased blood pressure upon standing). It belongs to a family of drugs called the alpha-adrenergic drugs and works by stimulating nerve endings to increase blood pressure. Several small studies have shown it is effective in controlling symptoms due to orthostatic hypotension. Because of potentially serious side effects midodrine should only be used in patients who have severe, life-style limiting symptoms of orthostatic hypotension that have failed to respond to conservative treatment measures. The main side effect of midodrine is hypertension (high blood pressure) in the supine (lying) position. This may be manifest by blurred vision, headache, or increased awareness of the heart beat.

Drugs that may interact with midodrine are as follows:

- o Digoxin (Lanoxin)-May increase effects on the heart

- o Steroids (e.g., Florinef) and some cold medications (e.g. ephedrine, phenylephrine, phenylpropanolamine, or pseudoephedrine) - may increase effects on blood pressure.

The usual dosing for adults is 10 mg 3 times a day in 4 hour intervals with the last dose to be taken no later than 6 pm. In addition one should avoid taking it prior to periods where supine posture is expected.

Potential side-effects that you should notify your doctor about include:

Blurred vision, cardiac awareness, headache, and/or pounding in the ears. Fainting; increased dizziness; slow pulse.

Other less serious side effects that may occur include:

More common

Burning, itching, or prickling of the scalp; chills; goosebumps; urinary frequency, retention, or urgency.

Less common

Anxiety or nervousness; confusion; dry mouth; flushing; headache or feeling of pressure in the head; skin rash.

Rare

Backache; canker sores; dizziness; drowsiness; dry skin; leg cramps; pain or sensitivity of skin to touch; stomach problems such as gas, heartburn, or nausea; trouble in sleeping; trouble seeing; weakness.

WARNING: Because ProAmatine® can cause marked elevation of supine blood pressure, it should be used in patients whose lives are considerably impaired despite standard clinical care. The indication for use of ProAmatine® in the treatment of symptomatic orthostatic hypotension is based primarily on a change in a surrogate marker of effectiveness, an increase in systolic blood pressure measured one minute after standing, a surrogate marker considered likely to correspond to a clinical benefit. At present, however, clinical benefits of ProAmatine®, principally improved ability to carry out activities of daily living, have not been verified.

Relevant recent research data

Integr Physiol Behav Sci 2000 Jul-Sep;35(3):208-11

Effects of the Medical Resonance Therapy Music on haemodynamic parameter in children with autonomic nervous system disturbances.

Sidorenko VN.

Mother and Child Health Institute of the Ministry of Health, Minsk, Belarus.

The present investigation is dedicated to the effects of the Medical Resonance Therapy Music (MRT-Music) on basic haemodynamic parameter in children with transient arterial hypertension due to disturbances of the autonomic nervous system with different degrees of initial sympatheticotonia. After the nuclear accident at Chernobyl many children developed blood pressure too high for their age norm. Having already observed a decrease in high blood pressure in pregnant women during Medical Resonance Therapy Music (Gerasimovich, Einysh, 1999; Gerasimovich, Sidorenko, 1995; Sidorenko, Tetiorkina, Korotkov, 1997) we studied the effects of the Medical Resonance Therapy Music (MRT-Music) on such children-with very positive results: the treatment with the music preparations demonstrated a clear sympatholytic effect and led the disturbed haemodynamic state back to its healthy age norm.

Arch Phys Med Rehabil 2000 Nov;81(11):1494-7

Blood pressure response to acupuncture in a population at risk for autonomic dysreflexia.

Averill A, Cotter AC, Nayak S, Matheis RJ, Shiflett SC.

Kessler Institute for Rehabilitation, East Orange, NJ, USA.

OBJECTIVE: To determine whether acupuncture can lead to autonomic dysreflexia (AD) when used to treat chronic pain in individuals with spinal cord injury (SCI). **DESIGN:** Acupuncture analgesia study. **SETTING:** Medical rehabilitation research center. **PARTICIPANTS:** Fifteen participants with post-SCI chronic pain who were at risk for AD (ie, SCI at or above T8). **INTERVENTIONS:** Half-hour acupuncture treatment sessions twice a week for 7.5 weeks, for a total of 15 treatments. Acupuncture needles were inserted both above and below the patient's spinal lesion level. Blood pressure (BP) was measured before and after acupuncture treatments. **MAIN OUTCOME MEASURES:** Systolic BP (SBP) and diastolic BP (DBP). Participants monitored for signs and symptoms of AD. **RESULTS:** On average, SBP and DBP remained stable across all 15 treatment sessions. None of the participants experienced any symptoms of AD. However, examination of individuals' BP readings indicated acute elevations (20 mmHg or higher) in SBP for 3 of the 15 participants. **CONCLUSIONS:** Although none of the 15 participants who were at risk for developing AD developed symptoms consistent with this diagnosis, 3 displayed an acute elevation in SBP, suggesting a pattern of imminent AD. Comorbid hypertension appeared to contribute to the elevation in 1 patient. Therefore, careful monitoring of patients with SCI or hypertension during acupuncture treatments is advisable.

Instr Course Lect 2000;49:549-57

Reflex sympathetic dystrophy: alternative modalities for pain management.

Gellman H.

UAMS Department of Orthopaedic Surgery, University of Arkansas, Little Rock, USA.

For the patient presenting with early symptoms (< 6 months) I usually start treatment with a dose pack of methylprednisolone, analgesics, and daily occupational/physical therapy for 2 weeks (Fig. 2). If they do not respond within the first week, I add stellate ganglion blocks and acupuncture to the treatment regimen. For patients presenting with established chronic pain, I immediately start them on a dose pack of methylprednisolone for 1 to 2 weeks, a nonsteroidal anti-inflammatory such as indomethacin, 50 mg 3 times a day for 10 days and then switch to 75 mg twice daily until there is a response. Amitriptyline is helpful for sleep and depression and also has a beneficial effect on blood flow. Calcium channel blockers (nifedipine) may help improve peripheral circulation by its effect on vascular smooth muscle. In this patient group, I almost always start stellate ganglion blocks on the first visit. I have the patient try at least 2 blocks before deciding whether or not blocks are helpful. Many patients will not respond to the first block, but will start to respond after the second block. If the blocks are helping, I recommend 3 blocks a week, every other day for 3 weeks. Patients get the most benefit from their blocks if they have occupational or physical therapy immediately following the block. Surgical sympathectomy may be helpful but only in patients who have responded to sympathetic blockade.

Clin Auton Res 1999 Aug;9(4):165-77

Sympathetic skin response following thermal, electrical, acoustic, and inspiratory gasp stimulation in familial dysautonomia patients and healthy persons.

Hilz MJ, Azelrod FB, Schweibold G, Kolodny EH.

Department of Neurology, New York University Medical Center, New York, USA.

To determine whether sympathetic skin response (SSR) testing evaluates afferent small or efferent sympathetic nerve fiber dysfunction, we studied SSR in patients with familial dysautonomia (FD) in whom both afferent small and efferent sympathetic fibers are largely reduced. We analyzed whether the response pattern to a combination of stimuli specific for large or small fiber activation allows differentiation between afferent and efferent small fiber dysfunction. In 52 volunteers and 13 FD patients, SSR was studied at palms and soles after warm, cold and heat as well as electrical, acoustic, and inspiratory gasp stimulation. In addition, thermal thresholds were assessed at four body sites using a ThermoTest device (Somedic; Stockholm, Sweden). In volunteers, any stimulus induced reproducible SSRs. Only cold failed to evoke SSR in two volunteers. In all FD patients, electrical SSR was present, but amplitudes were reduced. Five patients had no acoustic SSR, four had no inspiratory SSR. Thermal SSR was absent in 10 patients with abnormal thermal perception and present in one patient with preserved thermal sensation. In two patients, thermal SSR was present only when skin areas with preserved temperature perception were stimulated. In patients with FD, preserved electrical SSR demonstrated the overall integrity of the SSR reflex but amplitude reduction suggested impaired

sudomotor activation. SSR responses were dependent on the perception of the stimulus. In the presence of preserved electrical SSR, absent thermal SSR reflects afferent small fiber dysfunction. A combination of SSR stimulus types allows differentiation between afferent small or efferent sympathetic nerve fiber dysfunction.

J Hand Ther 1996 Oct-Dec;9(4):367-70

What makes treatment for reflex sympathetic dystrophy successful?

Hareau J.

Hand and Arthritis Rehabilitation Clinic, Montevideo, Uruguay.

Therapists throughout the world find it challenging to treat and rehabilitate patients with reflex sympathetic dystrophy. An insufficient understanding of the disease process often hinders the diagnosis, causing the patient unnecessary pain and distress. This paper presents effective diagnostic and treatment methods that emphasize patient trust as well as relaxation and range-of-motion exercises. The paper describes the cases of 120 women, aged 35 to 75 years, and 30 men, aged 30 to 60 years. The condition was diagnosed in these patients three months after the onset of primary symptoms and was successfully treated.

Acta Paediatr Jpn 1989 Aug;31(4):500-3

Autogenic training as an effective treatment for reflex neurovascular dystrophy: a case report.

Kawano M, Matsuoka M, Kurokawa T, Tomita S, Mizuno Y, Ueda K.

A 15-year-old girl complained of swelling and shooting pains in the right upper extremity, which had bothered her for seven months. Physical examination revealed swelling, cyanosis, weakness and hyperesthesia over the entire right upper extremity. Serological and biochemical data were within normal limits. She was diagnosed as having reflex neurovascular dystrophy (RND). Psychological problems with school and her family might have contributed to the pathogenesis of the disease. With autogenic training (AT), remission was obtained within eighteen months.

Am J Chin Med 1987;15(3-4):133-8

Efficacy of acupuncture treatment in autonomic ataxia.

Nishimoto T, Ishikawa T, Matsumoto K, Fujioka A.

Institute for Oriental Medicine, Hyogo, Japan.

Recently Coefficient Variation of R-R interval derived from patient's ECG is advocated

to be an objective and quantitative method of analyzing autonomic nerve function. In the present study, we used this method to make an evaluation of the acupuncture treatment on the patients suffering from autonomic ataxia. Twenty-one patients were admitted to this therapy according to the results of CMI (Cornell Medical Index) test. (4 males, 17 females, mean age was 49.9 y.o.) ECG machine was used to measure the R-R interval every 100 heart beats before and after the treatment, and through this survey, the mean R-R interval (mR-R) and Coefficient Variation (C.V. $SD/mR-R \times 100\%$) were obtained. Subjective complaints were obtained at the same time, too. The mR-R became extended in 14 out of 21 patients after treatment and mean value of mR-Rs after treatment was significantly increased than prior to treatment. (871.6 msec-before 918.3 msec-after p less than 0.05) As for C.V. the mean value was not markedly changed but the variance was decreased significantly (1.67-before 0.47-after p less than 0.025), and 60% of subjective complaints were improved after treatment. These results suggest that acupuncture therapy is effective on the patients who have been diagnosed as having autonomic ataxia by regulating autonomic nerve function.

Acupuncture may be tried to treat autonomic nervous system dysfunction including dysautonomia.

Literature Searched

Medline
MDConsult
78 Current Textbooks of Medicine
450 Current medical journals.
The Internet