DyAnsys

Detection, Monitoring and Treatment of Diabetic Autonomic Neuropathy

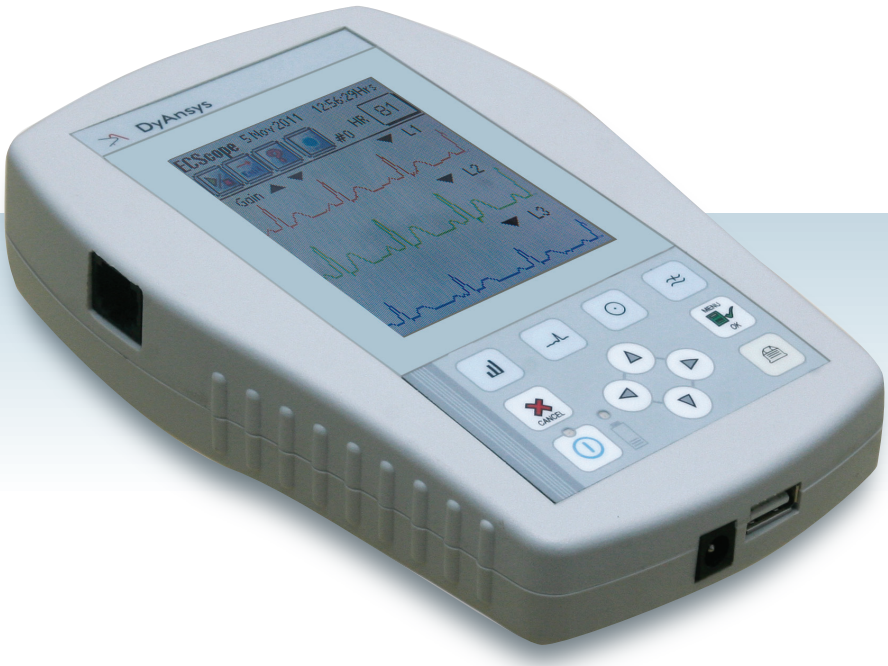


Table of Contents

Introduction

It gives me great pleasure to introduce this edition of "Detection, Monitoring & Treatment of Diabetic Autonomic Neuropathy" published by our Indian subsidiary DyAnsys India Pvt. Ltd.

Diabetes is one of the major health problems in the world today. There are a coupleof disturbing facts about diabetes. One, it is yet to have a cure. And two, the most critical factor about diabetes is not just the ailment, but the complications that accompany it. Of these, the biggest threat, which is fatal and still remains a mystery, is Diabetic Autonomic Neuropathy.

Why is so little known about DAN? For starters, there are no symptoms when it starts out as autonomic dysfunction. When it turns into autonomic neuropathy, there is a high probability that it affects one of the organs attached to the autonomic nervous system. It is then that symptoms show up – the symptoms exhibited by the affected organ. Very often, it is the heart that is affected and there are indications that 50% of those affected may lose their life to a 'silent heart attack' within five years. Silent because there are no chest pains associated with this, since the autonomic nervous system that provides the pain sensation is affected.

Exposing DAN for the damage that it can wreck remains one of the key focus areas for us at DyAnsys. Years of endeavour have resulted in a product that monitors the Autonomic Nervous System non-invasively. This can be used for early detection of autonomic dysfunction. The product was subjected to rigorous test-marketing amongst about 300 doctors in Southern India between 2006 and 2008. The experiences of these doctors yielded a lot of insights into the detection, monitoring and treatment of Diabetic Autonomic Neuropathy.

While this market research initiative was on in India, another development was taking place halfway across the world. The American Diabetes Association incorporated Heart Rate Variability testing for autonomic neuropathy in its standards of care in 2006. The recommendation was that the testing be done immediately upon detection of diabetes and repeated at least yearly thereafter if the indications were negative.

The whole area of autonomic neuropathy still remains obfuscated. We hope that with the publication of this booklet, we will do our part in shedding some light on this life-threatening complication.

A lot of thought has been put into this book to ensure that it's content proves to be relevant to a wide audience across the medical fraternity. We start out by reporting on the experiences of 45 doctors in India who have been using the ANSiscope and have been treating autonomic neuropathy. Their experiences have been shared and distilled into a protocol. These doctors are available for you to interact with - they will answer questions on the ANS Forum in the DyAnsys website (www.dyansys.com).

The next article is an in-house effort that brings together the current practice reported in the publications with appropriate references. This article was generated in response to the requests made by several doctors we had interacted with and who formed the primary target audience for our product, ANSiscope.

This is followed by an article that talks about using nutritional supplements (specifically L-Arginine based therapy) to treat autonomic neuropathy. It has been written by Dr. J. Joseph Prendergast of Palo Alto, CA, who has been using L-Arginine very successfully in his practice. Unfortunately, it is not very widely used, because it is not reimbursable by insurance (being a supplement). So it happens,that something that emanated out of a Nobel Prize (awarded in 1998 to Dr. Furchtgott, Dr. Murad and Dr.Ignarro) is not used in treatment in the US!

DyAnsys India publishes a newsletter called "Measure" that features a case study every month. The team has highlighted three case studies in this booklet by Dr. Shagul Hameet, Dr. Paneerselvam and Dr. Murugesan, three able doctors specialised in the field of treating autonomic neuropathy.

These articles are followed up with a host of publications presented at various conferences around the world. These present rare insights about autonomic neuropathy that we were able to gain because we have a product that, for the first time in the world, shows the behavior of the autonomic nervous system on a beat-by-beat basis. This allows us to put the spotlight on the ANS. The publications help put the valsalva maneuver under a microscope much like Dr. Harold Edgerton when he first discovered stroboscopic photography and was able to show a milk drop shaped like a crown! We trust that these articles will stimulate your interest and give you new insights into autonomic neuropathy.

Many doctors ask us why they should measure autonomic dysfunction when they are measuring HbA1C. One of our publications shows that there is really no correlation between HbA1C readings and autonomic dysfunction.

The other question that gets asked of us is how the measurement of autonomic dysfunction will change their treatment protocol. I can do no better than repeat what our Indian doctors have told us. They cite two reasons for using this. The first one is that by presenting a quantitative inference, they are able to elicit a lot more compliance from their patients. The wives are the ones that drive compliance at home! The second is that they finally have a measurement that enables them to estimate the effects of their treatment and determine its efficacy. This allows them to try many more things than they normally would.

Our expectation is that by doing our bit to provide the means that measure and publicise the successes, we can do our part in controlling, if not eliminating this fatal complication of diabetes.

Please do make the best possible use of this book. As always, your comments, suggestions and feedback can only aid us in our progress.

Srini Nageshwar
Los Gatos, CA

Treatment experiences of doctors in India

Detection, Follow up and Treatment of Autonomic Neuropathy

The experience of 45 doctors in India using the ANSiscope and making more than 32200 measurements over a period of 2 years.

Date:19/05/09 No. IN 0037

Question : After making the measurement with the ANSiscope, what do I do? How do I treat the patient?

The incidence of diabetes mellitus has been described as reaching epidemic proportions. It has been estimated that up to 50% of patients with type 1 or type 2 diabetes will have the complication of neuropathy. When the autonomic nervous system is affected, this can lead to a variety of symptoms such as tachycardia, orthostatic hypo-tension, gastroparesis, constipation, diarrhoea, faecal incontinence, impotence and bladder dysfunction, thus significantly affecting the quality of life of diabetic patients. Furthermore, the presence of autonomic neuropathy carries a significant increased risk of cardiovascular mortality. Deficits in the autonomic supply to the skin can also disrupt microvascular flow and impair sweating, contributing to the development of foot ulcers that occur as a consequence of the sensory deficits associated with sensory neuropathy in diabetes. Chronic foot ulcers that fail to heal are a major cause of nontraumatic amputation. There is thus a substantial clinical need to understand the mechanisms underlying autonomic neuropathy in diabetes and to find potential treatments that can prevent its development and treat the condition once it has occurred. Despite this, it has been observed that autonomic neuropathy is the least recognized and least understood complication of diabetes.

Heart rate variability is probably the most investigated and readily assessable measure of autonomic function. It reflects the balance between activity of the sympathetic and parasympathetic autonomic nervous system. As such, it is not a specific measure of underlying autonomic function, although it may be inferred that parasympathetic activity predominates during resting conditions and sympathetic activity during stimulated situations.

For calculating the heart rate variability which is an important and proven tool for evaluating Autonomic Dysfunction, scale covariance physics was applied to design the medical device called ANSiscope.

Autonomic dysfunction is measured as percentage of time where lack of interaction was observed between sympathetic and parasympathetic systems' beat per beat activities. A classification of the measurement is given among 5 groups, as Healthy (H), Early (E), Late (L), Advanced (A) and Most Advanced (MA).

By using this medical device, very early stage of autonomic dysfunction in diabetics can be differentiated more easily from healthy groups.

We collected the following information about the treatment for Diabetic Autonomic Neuropathy from the Doctors those who are using the ANSiscope. This represents the combined experience of 45 doctors making more than 32200 measurements by using the ANSiscope over the course of 2 years.

Diagnosis	Treatments	Suggestion
Early stage of autonomic dysfunction +		
Poor Glycemic control :	• Advised to follow Diet and exercise • Strict glycemic control with antidiabetic medications	Creating awareness about diabetes and its complications.
Good Glycemic Control:	Neurovitamins • Methycobalamin • Vitamin B1, B6, B12, Vitamin E or Multivitamins	Treatment/ Dose will be changed based on the health conditions, severity and other illness.
Peripheral Neuropathy:	• Glutamic acid • Alpha Lipoic Acid • Gama linolenic Acid • Gabapentin, Pregabapentin Or • Pregabalin • Benfothiamine	Referring patients who have more than 40% Autonomic dysfunction to specialists.
Late stage of autonomic dysfunction +		
Poor Glycemic control:	• Advised to follow Diet and exercise. • Strict glycemic control with antidiabetic medications.	Referring the patients who have more than 40% Autonomic dysfunction to specialists.
Good Glycemic Control and Peripheral Neuropathy:	• Neurovitamins • Alpha Lipoic Acid • Gama linolenic Acid • Gabapentin, Pregabapentin, or • Pregabalin • Benfothiamine	
Others: Renal disease, Cardiovascular disease, Diabetic Retinopathy, Foot ulcer.	Based on the findings, treatment will be given.	
Advanced and Most Advanced:		
Further Investigations to be done: • HbA1C, Blood sugar test. • Lipid profile Test • Kidney Function Test • Echo Test TMT...	If there is/are any abnormal findings, patients will be referred to a specialist.	

NOTE:

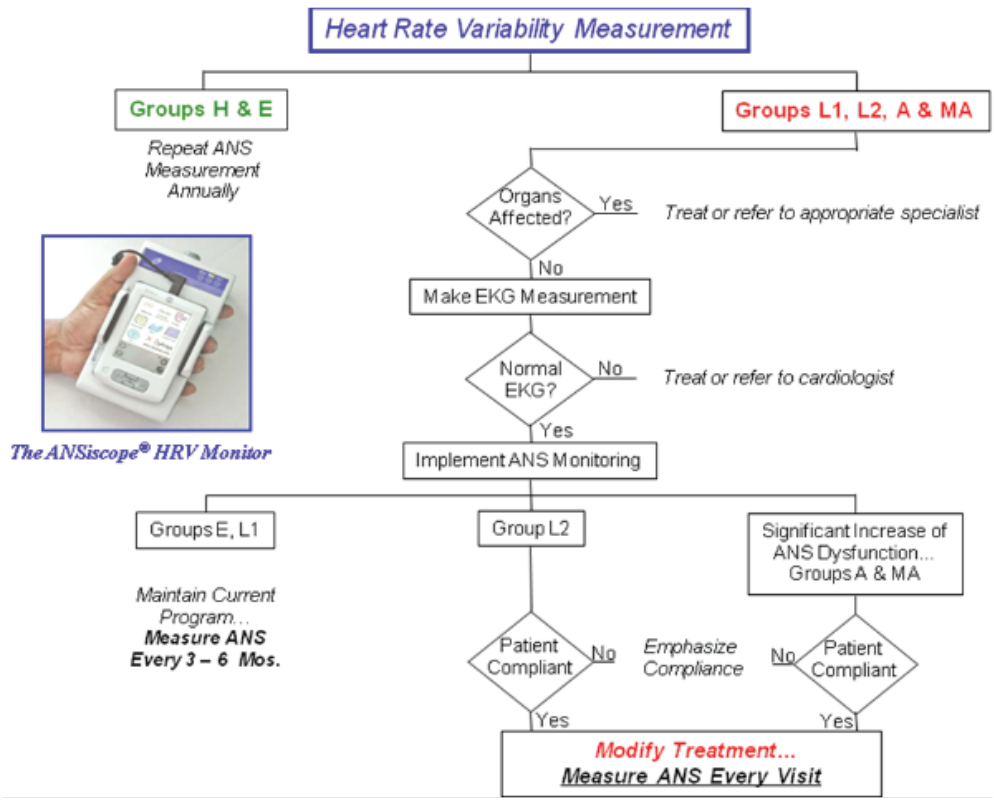
Educating the patients about the Diabetic autonomic neuropathy is the main part of the treatment. So the patients will be free from the tensions related to disease condition.

Review of material available in publications

Detection, Monitoring and Treatment of Autonomic Neuropathy

Implement ADA Standard of Care

The American Diabetes Association (ADA) incorporated Heart Rate Variability testing for autonomic neuropathy in its standards of care in 2006. The flowchart shown below indicates the diagnosis and the way ahead for patients who are classified in various stages of automonic neuropathy.



The prescribed course included heart rate measurement and ANS monitoring depending on the Group.

The recommendation was that the testing be done immediately upon detection of diabetes and repeated at least yearly thereafter if the indications were negative.

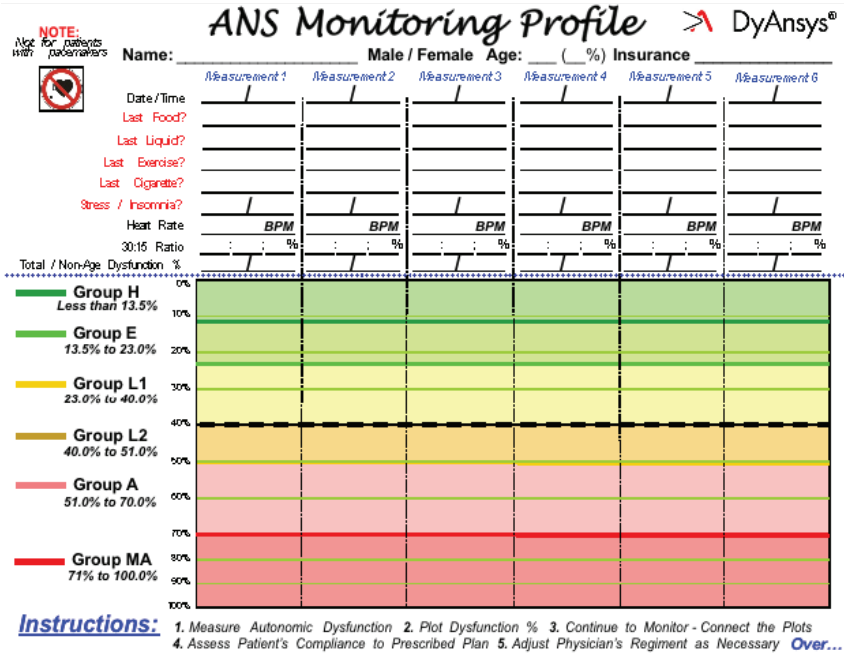
Legend for Groups:

H: Healthy	**L1: Late1**	**A: Advanced**
E: Early	**L2: Late2**	**MA: Most advanced**

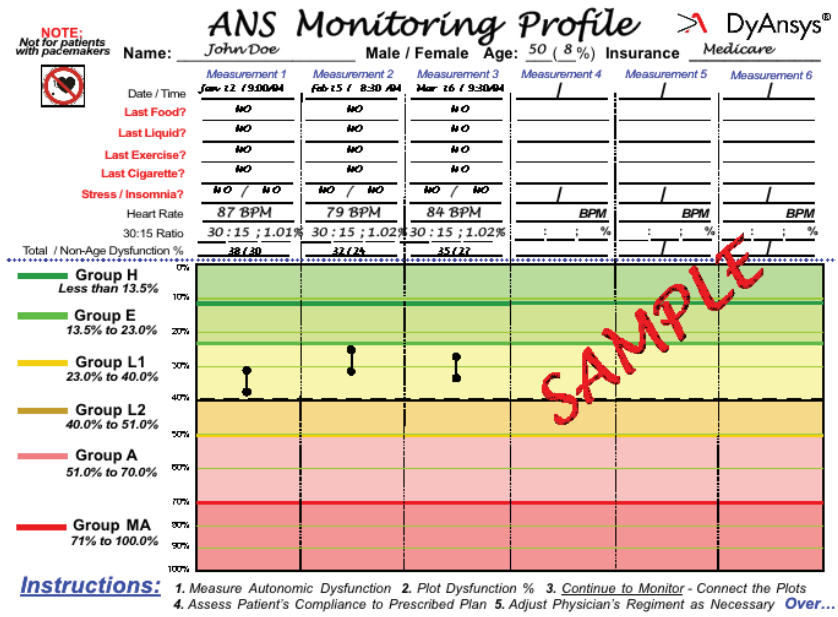
NS Monitoring Profile

Measurements for various groups were recorded in a format as shown below. Various factors like date, time, the conditions under which the measurements were taken and heart rate were noted for each measurement.

The format employs a colour code that goes from green to indicate healthy (Group H) to red, which is indicate of the most advanced stage (Group MA).



The following is a sample of the measurements recorded for a fictitious patient named John Doe, male aged 50, during his ANS monitoring. The sample shows three measurements that were recorded in regular intervals of 4-5 weeks.



Dysfunction percentage calculation

The dysfunction value achieved here is 38%. In this case, the actual reading displayed on the device would be 30. The age of the patient would then be taken into account and an additional 8% would be added if the patient is 50 years or older, which is the case in this sample.

Hence the dysfunction percentage is 38, which is 30% (recorded) plus 8% (added).

Likewise, the dysfunction percentage for the other two measurements will work out to:

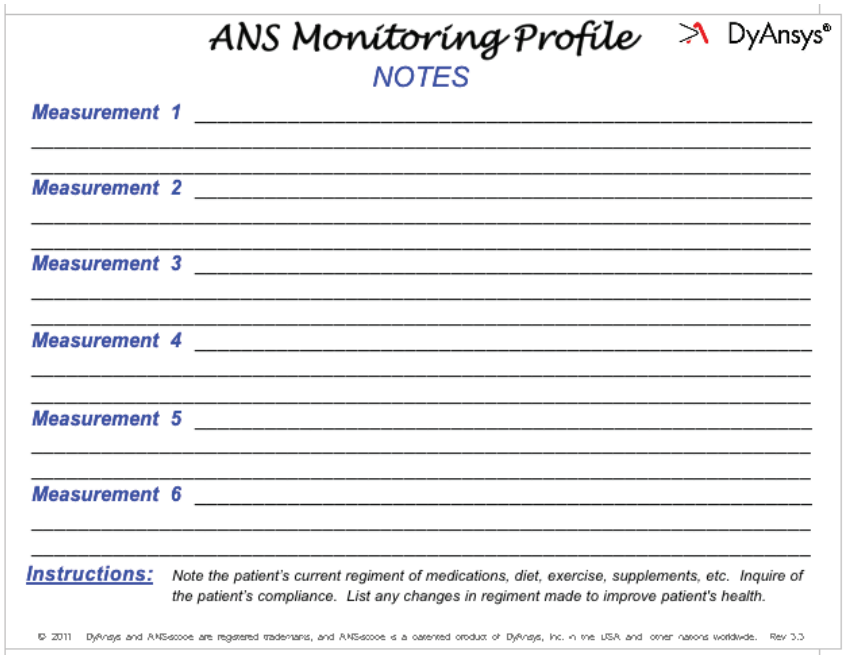
Measurement 2

Dysfunction percentage: 32 (24 + 8)

Measurement 3

Dysfunction percentage: 35 (27 + 8)

After the readings are complete, inferences are made in the form of notes in the format shown below.



ANS Monitoring Profile DyAnsys®

NOTES

Measurement 1 _____

_____

_____

Measurement 2 _____

_____

_____

Measurement 3 _____

_____

_____

Measurement 4 _____

_____

_____

Measurement 5 _____

_____

_____

Measurement 6 _____

_____

_____

Instructions: Note the patient's current regiment of medications, diet, exercise, supplements, etc. Inquire of the patient's compliance. List any changes in regiment made to improve patient's health.

Possible Treatment

The following are the clinical manifestations, their consequences and treatment prescribed for Cardiovascular Autonomic Neuropathy Due to Diabetes Mellitus.

Doctor: By Raelene E. Maser PhD., M. James Lenhard M.D., FACE, FACP

Glycemic Control	• Fair Glycemic Control (<8.4%) • Intensive Insulin Therapy
Anti-Oxidants	• 800 mg/d Alpha Lipoic Acid • Vitamin E (<400 IU/d)
ACE Inhibitors	• Quinapril
Angiotensin Type 1 Blockers	• Losartan 100 mg
Aldosterone Blockers	• Spironolactone (maybe disease specific) • Verapamil (with limitations)
Beta Blockers	• Metoprolol (with ramipril) • Metformin

Table 1: Autonomic Imbalance (Autonomic Dysfunction) Can Be Treated Using Common Medications

Agent	Nervous System Affected	Primary Site of Action	Primary Effect
Beta-1 adrenergic antagonists*	↓ Sympathetics	Heart	↓ Heart rate
Alpha-1/2 antagonists*	↓ Sympathetics	Peripheral vasculature	↓ Blood pressure
Angiotensin–renin antagonists	↓ Sympathetics	Kidneys	↓ Blood pressure
Calcium channel antagonists	↓ Sympathetics	Heart	↓ Blood pressure
Beta-2 adrenergic agonists	↑ Sympathetics	Lungs	↑ Air flow
Alpha adrenergic agonists	↑ Sympathetics	Vasculature	Constrict vasculature
Cholinergic antagonists	↓ Parasympathetics	Entire body	↓Parasympathetic activity
Cholinergic agonists	↑ Parasympathetics	Entire body	↑Parasympathetic activity

** These categories can include combination alpha/beta antagonists such as Carvedilol.*

Source: Autonomic Neuropathy Is Treatable

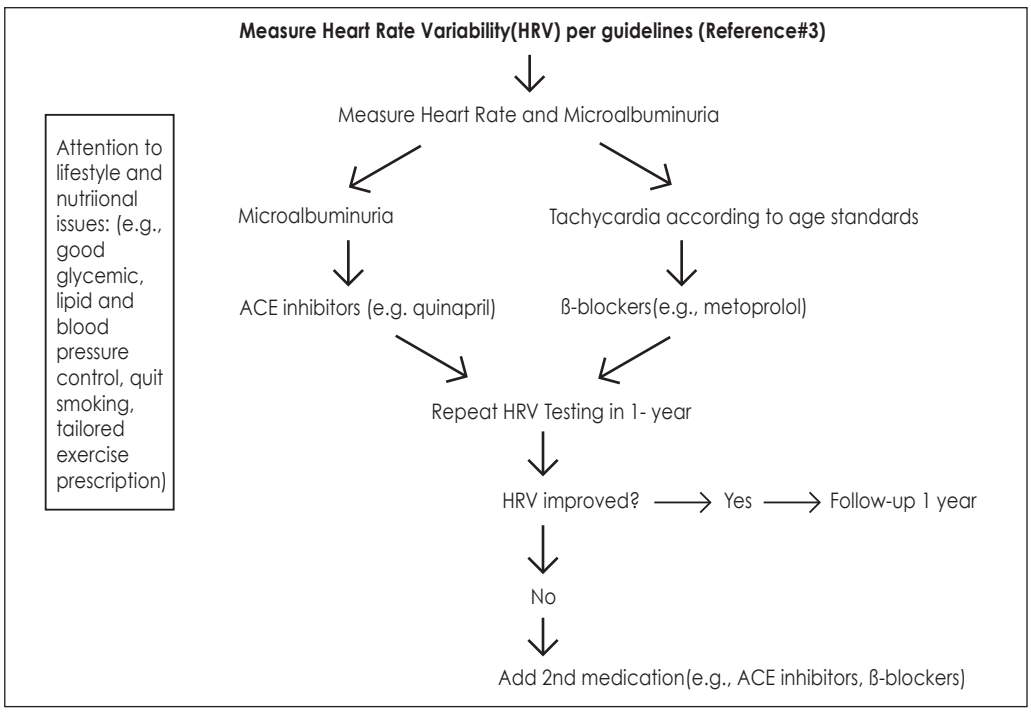
Aaron I Vinik, MD, PhD, FCP, FACP and Gary L Murray, MD, FACC, FACA, FASNC, FASCI, FASA; "Touch Briefings," 2008, pgs 82-84

Source: Autonomic Neuropathy Is Treatable

Aaron I Vinik, MD, PhD, FCP, FACP and Gary L Murray, MD, FACC, FACA, FASNC, FASCI, FASA; "Touch Briefings," 2008, pgs 82-84

The treatment also takes into account lifestyle issues and the right kind of nutrition for the patient.

As recommended by the ADA, Heart Rate Variability (HRV) is tested at regular intervals. In this case, it is done after a year of the previous testing and measurement.



Potential for Reversal of CAN

Several studies have reported that it is possible to improve HRV. In patients with minimal abnormalities, endurance training under strict supervision and lifestyle intervention associated with weight loss improve HRV.

Johnson et al have reported improved LV unction in patients with diabetic autonomic neuropathy (DAN) by using an aldose reductase inhibitor, but this still needs to be shown on a larger scale. Surprisingly, LV ejection fractions improved without a change in quantitative autonomic function test scores.-Blockers such as bisoprol improved HRV in heart failure.96 The addition of spironolactone to enalapril, furosemide,and digoxin in patients with heart failure improved sympathovagal balance.97 Angiotensin-converting enzyme (ACE) inhibition with quinapril increases total HRV and improves the parasympathetic/ sympathetic balance in patients with mild but not advanced autonomic neuropathy.98 ACE inhibition improves the prognosis of chronic heart failure, 99 but plasma concentrations of angiotensin 11 remain elevated,100 which may be related to non-ACE pathways that convert angiotensin 1 to angiotensin 11.101,102 Hence, addition of an angiotensin receptor blockade may overcome this problem,103 ostensibly effecting greater blockade of the renin–angiotensin–aldosterone system.101 Indeed, there are now several reports of beneficial effects on hemodynamic and neurohumoral effects of adding losartan,104 valsartan,105 or candesartan106 to an ACE inhibitor.

To investigate the effect of ACE inhibition or angiotensin receptor blockade and their combination on both DAN and LVDD in asymptomatic patients with diabetes, Didangelos et al106a examined 62 patients (34 women) with long-term diabetes mellitus (24 with type 1 diabetes mellitus and DAN). The patients, who were aged 51.713.9 years and were free of coronary artery disease and arterial hypertension at baseline, were studied for a 12-month period. Early ACE inhibition or angiotensin receptor blockade improved both DAN and LVDD after 1 year of treatment in asymptomatic patients with type 1 or 2 diabetes mellitus. The combination may be slightly better than monotherapies on DAN and LVDD auguring well for the patient with established CAN. The clinical importance of these effects should be validated by larger studies, however. Improvement in glycemic control reduces the incidence of CAN and slows the progression thereof.107 Glycemic control with a reduction of HbA1c from 9.5 to 8.4 has also been shown to improve HRV with mild autonomic abnormalities; this was not so in cases of advanced autonomic abnormalities.108 The use of aldose reductase inhibitors such as sorbinil improved resting and maximum cardiac output, and palrestat improved MIBG uptake and HRV in patients with mild abnormalities but not in those with advanced CAN.109 The most salutary lesson, however, derives from the Steno memorial study by Gaede et al,110 in which intensive multifactorial management aimed at control of BP, lipids, HBA1c, use of aspirin, vitamins E and C, and ACE inhibitors reduced CAN by 68%. Thus, it is important to diagnose CAN because the outlook is not as dismal as was once perceived; there are now symptomatic therapies that can reorient the functional abnormalities toward improved function, as well as herapies that provide prospects for reversal.

Screening - Diabetic Autonomic Neuropathy

How does one diagnose and treat Diabetic Automonic Neuropathy? This is how:

Maintain Tight Glycemic Control

For All Diabetic Patients:

Maintain aggressive control of blood glucose, hemoglobin A1c, blood pressure and lipids with pharmacologic therapy and lifestyle changes.

Screening

- When to begin screening:
  - Five years after diagnosis of type 1 diabetes
  - At the time of diagnosis of type 2 diabetes
- Ask patient about symptoms
- Examine patient for signs
- Test patient for heart-rate variability
  - If negative: Repeat yearly
  - If positive: Apply appropriate diagnostic tests, treat symptoms

Treatment for Diabetic Autonomic Neuropathy

SYMPTOMS	TESTS	TREATMENTS
Cardiac	Multigated angiography (MUGA) Thallium scan 123I metaiodobenzylguanidine (MIBG) scan	ACE inhibitors Beta-blockers Antioxidants Aldose reductase inhibitation
Postural hypotension	Measure blood pressure standing and supine Measure catecholamines	Supportive Garments Clonidine Midodrine Octreotide
Gastrointestinal	Emptying study Barium study Endoscopy Manoometry Electrogastrogram	Prokinetic agents Antibiotics Bulking agents Tricyclic antidepressants Pancreatic extracts
Sexual dysfunction	Penile-branchile pressure index Nocturnal penile tumescene	Sex therapy Psychological counseling Sildenafil Prostaglandin E1 Injection Device or prosthesis
Bladder dysfunction	Cystometrogram Postvoiding sonography	Bethanechol Intermettent catheteriazatio
Sudomotor (sweating) Dysfunction	Quantitative sudomotor axon reflex Sweat test Skin blood flow	Scopolamine Glycopyrrolate Botulinum toxin Vasodilators

Follow-up
Monitor every year for response to treatment

Recognizing and Treating Diabetic Autonomic Neuropathy
Aaron I. Vinik, MD, PhD, Tomris Erbas, MD

Experience with treatment with arginine therapy

– Dr. J. Joseph Prendergast, Palo Alto, CA

Ask most people with diabetes what neuropathy means and they'll quickly refer to symptoms of burning feet or numbness in the extremities. But these well-known manifestations of peripheral sensory neuropathy only tell half the story; in fact, as many as 60 percent of people with diabetes may suffer from autonomic neuropathy, another less-mentioned form of peripheral neuropathy. And while autonomic neuropathy may actually be considerably more deadly than its more familiar cousin, awareness of the condition and its dangers is only beginning to grow among doctors and patients alike.

While diabetic sensory neuropathy damages the sensory nerves in the extremities, diabetic autonomic neuropathy involves damage to the nerves serving the heart, all internal organs, and other processes that are not under direct conscious control. Impairment of the nerves serving the bladder or genitalia may cause urinary incontinence or erectile dysfunction. Sweat gland function may be affected, leading to uncontrolled perspiration, or a lack of it, resulting in overheating and dry skin. Autonomic neuropathy may also affect the nerves that internally sense blood pressure, leading to blood pressure that is too high or too low. Yet another complication is gastroparesis, a dysfunction of the stomach's autonomic nerves that may lead to slowed digestion, bloating, constipation, diarrhea, nausea, and vomiting.

Recent research indicates that autonomic neuropathy's most common and life-threatening consequences may be cardiac. Cardiovascular autonomic neuropathy can affect both heart rate control and cardiovascular dynamics. Add these effects to the already-serious tendency of diabetes to raise blood lipids and you have a condition ripe for disaster. Studies indicate that the onset of later-stage, symptomatic diabetic autonomic neuropathy is associated with a 50 percent mortality rate over the following five years.i

Early detection and intervention are of prime importance in heading off the potentially serious consequences of autonomic neuropathy. Yet surveys indicate that as few as 8 percent of diabetes patients know what autonomic neuropathy is, and only 2 percent believe they have undergone screening. ii To compound the awareness problem, diabetic neuropathy has a slow and insidious onset, and many patients may suffer from the condition unknowingly for years. Case reports abound in which autonomic neuropathy has gone undetected in patients with other chronic conditions such as Parkinson's disease. Studies indicate that as many as 60 percent of all people with diabetes have some form of neuropathy, although an estimated 30 to 40 percent of those are in the pre-symptomatic stage and are therefore unlikely to know of their condition.1

In our practice, we make a concerted effort to quickly identify patients with pre-symptomatic and symptomatic autonomic neuropathy, and then use a variety of interventions to get their condition under control. We routinely measure patients' heart rate variability, which research shows can help detect diabetic autonomic neuropathy in its early presymptomatic stages.

The American Heart Association and the American Association of Clinical Endocrinologists both recently declared heart rate variability as a recommended test for detecting autonomic dysfunction in diabetesiii. Heart rate variability testing has previously been limited to the research lab setting due to the fact that it called for customized and computerized analysis of electrocardiograms, but today physicians nationwide can incorporate a heart rate variability test, such as the DyAnsys System, into a single office visit.

Using the DyAnsys test, we look at heart rate variability response. We are able to track patients' heart rate variability over an extended period of time. With these and other test results as our guide, we can quickly set an individualized treatment regimen. People with diabetes should be tested for heart rate variability at least once per year as part of their personal diabetes management routine.

More than 25% of diabetics achieve heart rate variability test scores below the 5th percentile (and therefore abnormal) for a healthy population. Therefore, this form of testing identifies a large group with autonomic dysfunction2.

When we detect diabetic autonomic neuropathy, the first and most important focus of treatment is blood sugar control. We find that many of our patients, particularly those with Type

2 diabetes, have not been under tight control for some time. Until recently, researchers were unsure as to whether high blood sugar levels were actually responsible for complications of diabetes. In 1993, the results of the Diabetes Control and Complications Trial (DCCT) largely put those doubts to rest. The nationwide study looked at 1400 people with Type 1 diabetes, half of whom followed their regular self-treatment regimen, and half who adopted a tighter standard for blood sugar control. Early signs of kidney and eye disease were significantly lower in the tighter-control group, and their rates of diabetic neuropathy were 60 percent lower3. Tight blood sugar control appeared so beneficial that the study was stopped a full year early so that the results could be announced.

Tight blood sugar control is now the standard treatment for Type 1 diabetes, and additional studies from Japan and Europe indicate that controlling blood sugar slows the development of complications in people with Type 2 as well. Patients with Type 2, however, must walk a finer line; tight blood sugar may have the somewhat paradoxical effect of increasing weight in many patients, and weight gain exacerbates diabetes. Maintaining healthy blood sugar levels while controlling or reducing weight remains a challenge for many people with diabetes. Most diabetologists recommend that people who want to avoid neuropathy should work with an endocrinologist, a dietician and a diabetes nurse educator.

Those without diabetes begin treatment with ProArgi9 plus at a double dose and Mistica at a double dose. Retesting beginning at 30 days sets the pace for the time for reversal. If the situation is not progressing fast enough, the addition of Core Greens is necessary. Treatment continues until normal and then checked each 6 months until one year. Then it is checked yearly.

The consistent yearly check is necessary since the etiology is unknown. With diabetes we have a traditional series of measurements where all the neuropathy can be watched in addition to the autonomic neuropathy. New medications as Byetta and Januvia appear to add efficiencies to diminishing the swings of blood glucose and may add to success.

Type one diabetes can use all these therapies but in the past we have developed proven therapies that have shown to be quite useful.

We begin our intervention by introducing the patient to the use of an insulin pump, which we have found extremely effective in helping to control even the most "brittle" diabetic patients. The pump can deliver a slow, steady dose of insulin, mimicking the role of the pancreas, which normally supplies the body with insulin. At the same time, the pump can be set to deliver large "bolus" doses of insulin at mealtimes, again, just as the pancreas does. Our goal is to consistently bring patients' glycoslated hemoglobin levels below 7.0%, and using the pump, we can usually achieve this within one month.

We also use a number of other interventions to ward off coronary artery disease, including administration of 800 mg of the antioxidant vitamin E per day, and l-arginine, an amino acid that smoothes the internal lining of blood vessels.

Perhaps the most important things we can do for our patients with diabetes are to make them aware of autonomic neuropathy, to let them know whether they have it, and to help them keep blood sugar levels in an acceptable range. Doing so not only helps reduce the risk of heart disease, but also lowers the risk of diabetic eye, kidney and nerve disease, each of which patients dearly want to avoid.

Diabetic autonomic neuropathy has been called a "silent killer," because so few patients realize that they suffer from it, and yet its effects can be so lethal. With a brief, 15-minute test that we can administer in the office, and some relatively modest interventions, we can help many patients live longer, healthier lives.

Dr. Joseph Prendergast, M.D. F.A.C.P. F. A.C.P. is an endocrinologist and founder of Endocrine Metabolic Medical Center, Palo Alto, California 94306

1 Ziegler D. Diabetic cardiovascular autonomic neuropathy: prognosis, diagnosis and treatment. Diabetes Metab Rev 10:339-383, 1994

2 Ewing D, Martyn R, Young R, and Clarke B. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care 8:491-498, 1985.

3 The DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The New England Journal of Medicine 329: 977-986, 1993.

i) Vinik, AI, MD, PhD, and Suwanwalaikorn, S, MD: Autonomic Neuropathy, In deFronzo, R.M. (ed). Current Therapy of Diabetes Mellitus. Yearbook Inc. 1997; 165-176.

ii NFO Research, Inc.: The Diabetic Autonomic Neuropathy Awareness Survey, commissioned by Boston Medical Technologies, Wakefield, Massachusetts. March 2001.

iii The American Association of Clinical Endocrinologists Medical Guidelines for the Management of Diabetes Mellitus: The AACE System of Intensive Diabetes Self-management – 2000 Update, Endocrine Practice 2000; 6(1): 43-84; American Heart Association, 1999. AHA Scientific Statement; Diabetes and cardiovascular disease. Circulation 100:1134-1146. ©

Case studies

The following section presents three case studies, all of which focus on autonomic neuropathy. In each of these cases, the diagnosis, treatment and inferences are presented. The role of the ANSiscope in observations and measurement of autonomic dysfunction is also seen.

Case Study I

The first case is by Dr. Shagul Hameet, MBBS, D.Diab., MHSC Diab., the founder of Raaja Multi Specialty Hospital located in Tirunelveli district in the state of Tamil Nadu, India. The case involves eighteen Type II and two Type I diabetic patients who were divided into three groups and treated for autonomic neuropathy.

Case Description

Eighteen Type II and Two Type I diabetic patients were presented to our diabetic center between July 2006 and Oct 2007.

The way ahead

All eighteen patients were advised to undergo strict diabetic control together with proven autonomic neuropathy adjunctive therapy like alpha-lipoic acid, methycobalamine and pre-gabalin/gaba pentin after autonomic neuropathy was detected with the ANSiscope.

Follow-up for all patients was scheduled on quarterly basis for effective monitoring and treatment.

Treatment

11 out of 20 patients, labeled as Group 1, were incubated with adjunctive therapy and diabetic control.

Four patients, labeled as Group 2, were incubated with adjunctive therapy but didn't adhere to diabetic control.

Five patients, labeled as Group 3, were not incubated with adjunctive therapy, but were under diabetic control.

Result

The reversals of autonomic neuropathy were found to be effective in Group 3 and very effective in Group 1, while nil improvement was observed in Group 2.

Inference

In conclusion to the above observation, anti-oxidants/neurovitamins enhance the reversal of autonomic neuropathy, while they are dysfunctional in the case of uncontrolled diabetes.

Of all treatments, lifestyle modification, exercise, and tight and stable glycemic control are probably the most important for halting, decreasing or preventing autonomic neuropathy. Supplementation is expected to be more effective when a deficiency in these micronutrients exists.

Neuropathies are the most common complication with type 1 and type 2 DM. In Type 1 DM, autonomic neuropathy typically becomes symptomatic after many years of chronic prolonged hyperglycemia. Conversely, patients with Type 2 DM may display instances of autonomic neuropathy after only a few years of known poor glycemic control – in certain cases, these patients already have autonomic neuropathy at the time of diagnosis.

ANSiscope – because early detection is the first step to cure

ANSiscope, a novel heart rate variability based testing equipment is quite a remarkable tool in diagnosing and monitoring autonomic neuropathy at pre-symptomatic stages. Measurement of HRV at the time of diagnosis of Type 2 DM and within 5 years after diagnosis of Type 1 DM (unless an individual has symptoms suggestive of autonomic dysfunction earlier) serves to establish a baseline, with which tests performed with 1-year intervals can be compared.

Regular HRV testing provides early detection and thereby promotes timely diagnostic and therapeutic interventions. HRV testing may also facilitate differential diagnosis and the attribution of symptoms (e.g., erectile dysfunction, dyspepsia and dizziness) to autonomic dysfunction. Finally, knowledge of early autonomic dysfunction with ANSiscope can encourage both the patient and physician to improve metabolic control and to use therapies proven to be effective for patients with autonomic neuropathy.

Case Study II

Dr. A Panneerselvam, M.D., D.Diab. is a renowned diabetologist who has received a lifetime achievement award in August 2007 from the Chengalpattu Medical College Alumni. After being an Assistant Professor of Diabetology in Kilpauk Medical College for over a decade, he has taken on a host of responsibilities, holding prestigious posts in several diabetes associations. Besides being a successful doctor, he is also a keen academic who has participated in various national and international conferences and has conducted several health education programmes and community health camps.

Case Description

This case deals with a 75 year old woman with diabetic complications and sugar levels that were over 200 mg for over five years.

Case Report

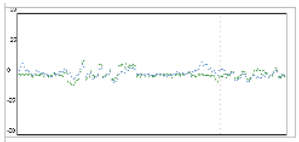
This case report involves a 75 year old female patient who was presented to our centre in Jan 2006. The patient has been a diabetic for over a decade and her blood sugar reports were more than 200 mg for the last 5 years.
On evaluation, she was found to have the following diabetic complications:

Case History

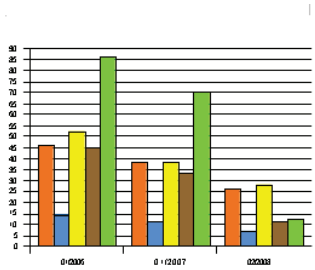
*Urea: 46mg, Creatinine: 1.4mg, Urine for Micro Albumin (UMA): 52mg, Vibration perception: 45 volts and ANSitest: 86 % (Most Advanced).
*Figure 1 shows the ANSitest report, indicating a most advanced stage of dysautonomia with full decoupling between the two subsystems of the autonomic nervous system (ANS).

Follow-up 1: 2007

The patient was placed under a prolonged programme of good diabetes control and satisfactory results soon followed. By Jan 2007, we were able to observe the initial reversal stage of autonomic neuropathy and other parameters.
*Urea: 38mg, Creatinine: 1.1mg, UMA: 38mg, Vibration perception: 33 volts and ANSitest: 70% (Advanced).
*Figure 2 shows the ANSitest report still indicating an advanced stage of dysautonomia, though sensible improvement can be observed in the reactivity of the sympathetic system.



Date	Urea(mg)	Creatinine(mg)	UMA(mg)	VPT(Volts)	ANSitest (%)
01/2006	46	1.4	52	45	86
01/2007	38	1.1	38	33	70
02/2008	26	0.7	28	11	12



10 unit = Creatinine (1 mg)

It appears that the ANSitest stands out as a new and unique test to pick up the presence of complications of diabetes and to assess regression of these complications towards normalcy. Patients with longstanding diabetes and hypertensive problems whose ANSitest report is over 60% have greater chances of developing cardio-respiratory arrest or respiratory failure during major surgical procedures. This can happen due to anesthesia or because of the procedure itself. In some cases, such patients can expire due to a sudden cardiac arrest and for a few of them, ventilator weaning procedure is not possible. It should be stated that among its numerous applications, the ANSiscope can be used for pre-anesthetic evaluation in cases of chronic diabetes and in cases of elderly people who are undergoing major surgery. Anesthetists and surgeons can then take precautionary measures.

The present case of neuropathy reversal makes a beautiful example of ANSiscope usage in the yearly follow-up of diabetics.

Case Study III

This case is presented by Dr. V Murugesan, MD (Retd) Professor of Medicine at Kilpauk Medical College and Superintendent, Govt. Hospital, Royapettah, Chennai, India. Besides offering a simple explanation to autonomic neuropathy, it deals with truncal ataxia.

Case Description

The following is a case involving truncal ataxia. Ataxia may primarily involve the trunk (truncal) and the patient may not be able to sit or stand unsupported (ataxia); truncal ataxia is usually due to midline cerebellar disorder – in other words, midline damage to the cerebellar vermis and associated pathways that leads to proximal musculature, especially when it involves gait stability.

Case History

A 71-year old male was presented to our clinic in May 2006 with the following findings:
CABG for IHD
Parathyroid adenoma surgery
Gall stones
Malabsorption syndrome
Hypothyroidism
ACEI induced cough (Ramipril)

Patient complaint

Swelling of legs during prolonged walking – however he was getting relief when he rested.
Difficulty in walking
Unsteadiness over the past week.

Diagnosis

Since the patient the patient had a previous history of cardiac complication, an ECG was taken in which the results were found to be normal. Based on the symptoms revealed by the patient, accompanied by Ramberg Test and tandem standing, it was observed that the patient exhibited severe disability when balancing the body without any support (Truncal Ataxia). Autonomic neuropathy was suspected as the patient had been a diabetic for 20 years. A dysautonomia test was performed using ANSiscope and the patient was found to be in the most advanced stage (76%).

Treatment

Focus on blood glucose control
Methycobalamine 500micro grams
Benfothimine 100 mg
Alpha lipoic acid 100mg..
A repeat assessment of autonomic dysfunction using ANSiscope on July 08, (a year after the patient was first diagnosed with truncal ataxia) showed that the patient was in 72% of DAN.

Observations

The following clinical and functional observations were made when the patient came back for a repeat assessment..

A.Clinical

Moderate improvement in standing and gait, except for occasional nocturnal attacks of dizziness at about 2:30am. These attacks were not accompanied by sweating and the patient responded to one or two sugar candies within 15 minutes.(The current status of the patient is that he is able to walk up to 20 minutes continuously). These clinical observations indicate that the patient is recovered from the progressive state of autonomic neuropathy.

B. Functional

A 4% reduction in degree of autonomic dysfunction from 76% to 72% was observed. The clinical improvement of the patient was found to be directly proportional to the function-wise measurement of the ANSiscope's output. This clearly indicates that further progression of autonomic dysfunction has been halted. This indicates that the chances of reversing the dysfunction level from its advanced and most advanced condition are less.