DIABETIC AUTONOMIC NEUROPATHY

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Autonomic neuropathy is a well-recognized complication of diabetes mellitus, particularly in those with long duration of diabetes and in association with peripheral dysfunction (1,2). Autonomic dysfunction in diabetes is common but, in sharp contrast, symptomatic autonomic neuropathy is rare as most patients remain asymptomatic. Abnormal cardiovascular tests are found in at least 16% of a diabetic population, although some have reported up to 80% (3). It is almost certainly much commoner in Type 1 diabetes mellitus where the prevalence rate is described to be 12% as compared to 0.5% of Type 2 diabetes mellitus patients as described by Neil (3).

Small fibre Neuropathy

There exists a distinct syndrome, in which selective damage to small nerve fibres causes some sensory and autonomic loss. Most patients are usually young insulin dependent diabetic subjects in their twenties and thirties often women. They develop symptomatic autonomic neuropathy, often with postural hypotension, abnormal sweating, increased blood flow in feet and gastroparesis and or diarrhoea, with Charcot arthropathy and foot ulceration. They have grossly abnormal autonomic function tests, loss of thermal sensation and increased peripheral blood flow. Despite their youth, many of these patients show medial calcification of the arteries in the feet, which may be a consequence of sympathetic (small fibre) denervation of the vessels (4). They do not experience numbness of their feet and they have normal touch sense and near normal vibration perception. This striking syndrome is highly destructive and it is speculative that an immunological attack may be the provocative agent.
Immunological Basis:

Immunological mechanisms may have a causative role in the genesis of symptomatic autonomic neuropathy. An auto-immune basis is suggested by the association with iritis, in about 33% of cases (5). The presence of auto antibodies to autonomic nervous tissue structure is a feature of patients with symptomatic diabetic autonomic neuropathy (DAN). It has not been established whether these auto-antibodies cause or contribute to, or simply reflect, nervous tissue damage. Researchers from department of Immunology, King’s College, London (6) tested serum samples for the presence of complement – fixing auto antibodies to adrenal medulla, vagus nerve and sympathetic ganglia cells and demonstrated the persistence of these antibodies in Type 2 diabetic with DAN. Barzilay et al (7) have reported an increased propensity of subjects with HLA DR3/4 to develop autonomic dysfunction and circulating immune complexes (Clq) have been found to be elevated (8) as well as activated lymphocytes (9). Reversal of autonomic neuropathy by immuno-suppression has also been attempted in the USA.

Consequences of Autonomic Dysfunction:

Diabetes can cause dysfunction of every part of the autonomic nervous system. The areas of dysfunction that are most important to the clinician included cardiovascular reflexes, gastro-intestinal function, genitourinary function and certain metabolic functions such as glucose counter regulation and awareness of hypoglycaemia. The clinical manifestations of DAN are tabulated in Table 1.

Table 1: Clinical manifestations of diabetic autonomic neuropathy

Cardiovascular:
Resting Tachycardia, exercise intolerance, cardiac denervation, orthostatic hypotension, heat intolerance, skin temperature reversal, dry skin and dependent edema

Gastrointestinal
Esophageal enteropathy, gastroparesis diabeticorum, constipation, diarrhoea, fecal incontinence.

Genitourinary
Neurogenic bladder, Impotence
Cystopathy, Retrograde ejaculation.

Sweating Disturbances
Areas of symmetrical anhydrosis, gustatory sweating.

Metabolic
Hypoglycemic unawareness, Hypoglycemia unresponsiveness, Hypoglycemia – associated autonomic failure (HAAF).
Pupillary
Decreased diameter of dark-adapted pupil
Argyll – Robertson type pupil.

Cardiovascular Abnormalities (CAN)

CAN is characterised by resting
Tachycardia, impaired exercise induced
cardiovascular responses, cardiac
denervation, orthostatic hypotension,
heat intolerance, impaired vasodilation and
impaired veno-arteriolar reflex (dependent
edema).

Resting Tachycardia

The basal heart rate is set by the
chronotropic properties of the heart
through its intrinsic pacemaker, the sinus
node. Autonomic influences on heart rate
under basal conditions, beat – to – beat
variations and changes associated with
breathing are mediated by the para-
sympathetic system.

The earliest manifestations of
impaired autonomic denervation of the
heart are due to vagal denervation. The
parasympathetic nerve fibres being longer
are affected before the sympathetic fibres
which are shorter. Frequently, a resting
tachycardia of > 90-100 beats/minute is
observed, and more rapid rates of up to
130 may occur. As the condition worsens,
this results in a fixed tachycardia
unresponsive to maneuvers. This is similar
to that following blockade with atropine
and propranolol. However, because
diabetics as a group have faster heart rate
than controls, resting tachycardia is not a
reliable indication of autonomic
neuropathy. Affection of the sympathetic
nervous system with postural hypotension
etc is usually a sign of poor prognosis. In
general, once DAN sets in, the mortality is
40-50% within 5 years.

Cardiac Denervation Syndrome:

A fixed pulse rate of 80 to 90 beats per
minute that is unresponsive to mild
exercise, stresses, or sleep indicates nearly
complete cardiac denervation (10). Cardiac
denervation is the cause for the increased
incidence of painless myocardial infarction
seen in diabetic patients (11). Twenty four
hour ambulatory ECG monitoring
provides a useful diagnostic information in
early detection and evaluation of silent
myocardial ischaemia in asymptomatic
diabetic patients (12). Treadmill testing is
also a useful procedure to diagnose silent
ischaemia, especially in diabetes. In our
study (13), 65 out of 139 TMT positive
cases (46.8%) had silent ischaemia. Since
myocardial ischaemia may not cause
typical anginal chest pain in diabetic
patients (14), severe coronary artery disease
may be clinically occult. Therefore, vague
thoracic or epigastric symptoms in a
diabetic patient may represent myocardial
ischaemia and should be regarded with a
high index of suspicion. Diabetic patients who are likely to have cardiovascular autonomic neuropathy should be strongly advised to have cardiac stress testing before undertaking an exercise program.

**Exercise intolerance:**

In normal persons, the ANS is important in the cardiovascular response to exercise. During the early stages of exercise there is a decrease in cardiac parasympathetic PNS activity (15) followed by an increase in vascular sympathetic nervous system activity (16). At maximum levels of exercise (near exhaustion) there is a release of epinephrine (17). These responses increase cardiac output, ejection fraction, blood pressure and heart rate and thus supply increased amounts of oxygen and nutrients needed by the brain and skeletal muscles. In diabetic patients evaluated by graded exercise, it was found that worse cardiovascular autonomic neuropathy, was associated with the more abnormal cardiovascular performance, systemic peripheral resistance and changes in heart rate. The increase in plasma norepinephrine during exercise was smaller in the patients with postural hypotension. Thus cardiovascular autonomic neuropathy appears to contribute to the poor exercise tolerance observed in many diabetic patients.

**Postural hypotension:**

On standing, about 700 ml of blood pools in the splanchnic bed and the legs and cardiac output decreases by 20-50%. Maintenance of normal blood pressure on standing depends on a reflex arc that involves afferent impulses to the heart and blood vessels, increasing sympathetic vasoconstrictor tone (especially in splanchnic bed and leg muscles), heart rate and myocardial contractility. If any part of this fails, postural hypotension results.

The syndrome of postural hypotension is characterised by posture related weakness, dizziness, visual impairment and presyncope. Although the definition of postural hypotension varies among investigators, it is generally accepted that a fall of 10 mmHg in diastolic blood pressure or 20 mmHg in systolic blood pressure is sufficient to establish the diagnosis. The diagnosis is made simply by measuring the blood pressure lying and standing. In some patients, the blood pressure does not fall immediately on standing and it should be measured after standing for two minutes. The differential diagnosis of postural hypotension include “idiopathic” postural hypotension of the elderly, which may be exacerbated by prolonged bed rest.
vasodilator and other drugs; dehydration, eg. following a period of badly controlled diabetes; the Shy-Drager syndrome and other conditions of autonomic failure.

Patients should be advised to get up slowly and to exercise the leg muscle before standing. Hypotensive drugs should be avoided and diabetic control improved to avoid polyuria and dehydration. Specific treatment included fludrocortisone and non-steroids antiinflammatory drugs. Midodrine, a somatostatin analogue octreotide causes vasoconstruction in splanchnic bed and may help in postural hypotension. Some severely affected cases have been helped by the use of "anti gravity suits", which compress the legs and increase venous return.

Assessment of Cardiovascular Autonomic Nervous System:

Unlike the peripheral, sensory motor nervous system in which individual nerves can be tested directly, the ANS is usually studied by observation of end-organ function. Many techniques have been used to assess the cardiovascular ANS. They are usually divided into tests of parasympathetic functions (Heart rate variability) and sympathetic function (blood pressure variation). We use a battery of seven tests to assess cardiovascular autonomic fibres and these are shown in Table 2.

Table 2: Normal values for autonomic nervous system test (Mohan et al 20)

<table>
<thead>
<tr>
<th>Coefficient of variation of RR</th>
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<tbody>
<tr>
<td><strong>Heart Rates</strong></td>
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<tr>
<td>Heart rate response to Valsalva</td>
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<tr>
<td>Heart rate variation during deep breathing</td>
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<tr>
<td>Heart rate response to standing</td>
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<tr>
<td><strong>Blood Pressure Tests</strong></td>
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<tr>
<td>Blood pressure response to standing (fall in systolic BP)</td>
</tr>
<tr>
<td>Blood pressure response to sustained handgrip (increase in diastolic BP)</td>
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<table>
<thead>
<tr>
<th>Control (mean ± SD)</th>
<th>Abnormal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate response to Valsalva</td>
<td>13.2 ± 5.0</td>
</tr>
<tr>
<td>Heart rate variation during deep breathing</td>
<td>11.3 ± 4.4</td>
</tr>
<tr>
<td>Heart rate response to standing</td>
<td>6.5 ± 2.4</td>
</tr>
<tr>
<td>Blood pressure response to standing (fall in systolic BP)</td>
<td>Less than 10 mm</td>
</tr>
<tr>
<td>Blood pressure response to sustained handgrip (increase in diastolic BP)</td>
<td>More than 16 mm</td>
</tr>
</tbody>
</table>
R-R Variation

It is a well known phenomena that RR interval shortens during inspiration and lengthens during expiration. This sinus arrhythmias (or beat-to-beat variation in RR interval) during quiet respiration has been used as an index of cardiac PNS activity since 1973. The difference between the maximum and minimum heart rates are recorded over a period of time during deep breathing at six breaths per minute. The co-efficient of R-R interval is also found, which is generated automatically in certain computerized electrocardiogram with an already in built programme. The co-efficient of variation is done both on supine position and standing position. In cardiovascular autonomic neuropathy the R-R variation is diminished and several cardiac autonomic neuropathy (CAN), a flat level with no R-R variation can also be obtained which signifies poor mortality rate.

Valsalva Maneuver:

The valsalva maneuver consists of forced expiration against a standardized resistance for a specified period of time. This maneuver was originally described by Antonia Valsalva, a surgeon from Bologna (18), in which the patient is asked to maintain a pressure of 40 mmHg while blowing into a mouth-piece connected to an mercury manometer. The Valsalva ratio is calculated which is the maximum heart rate during the Valsalva maneuver divided by the slowest heart rate after the Valsalva maneuver. The ratio of <1:10 is abnormal, 1:10 – 1: 20 is borderline and > 1:21 is defined as normal. Although it is a simple, non-invasive test, it may be less sensitive than the formal invasive testing and probably measures only the vagal part of the reflex. It has been shown to be very much reproducible and has been used successfully to predict premature demise (19). This test is effort dependent and therefore subjects can cheat and it should be avoided in patients with proliferative diabetic retinopathy where intra ocular pressures increases.

Cardiac Autonomic Dysfunction in South Indian Diabetics – Our Experience

The prevalence of cardiovascular autonomic dysfunction in Type 2 diabetes and fibrocalculous pancreatic diabetes was assessed by a standard battery of autonomic dysfunction tests (20). The study group comprised of 336 patients with Type 2 diabetes and 40 patients with FCPD. A battery of five standard tests of autonomic dysfunction, three tests of heart rate responses and two tests of blood pressure responses to different maneuvers were done using protocols recommended by Ewing and Clarke (21). The tests were
done in the morning in the basal state using a computerised electrocardiograph machine (Fakuda ME, Cardiosuny, Japan) with an in-built programme for performing computerized R-R interval analysis. The machine automatically calculates the mean of approximately 100 R-R measurements and provides the minimum R-R, maximum R-R and Coefficient of Variation (CV) of RR for each of the parameters used. For each test, the normal values of the CV of R-R were first determined in the control group and a value below 2SD of the mean control value was taken as an abnormal test i.e. indicative of autonomic dysfunction (Table 2).

Statistical analysis were done using SPSS programme (Version 4.0.1) on an IBM PC compatible computer. Multiple logistic regression analysis was done using autonomic dysfunction as the dependent variable and a host of independent variables including age, duration of diabetes, body mass index, systolic and diastolic blood pressure, HbA1c, lipid profile and other complications of diabetes.

Abnormalities of autonomic functions were detected in 120 Type 2 diabetes mellitus (35.7%) and 9 FCPD (22.5%). Below the age of 20 years, there was no evidence of autonomic dysfunction whether in Type 2 diabetes mellitus or in the FCPD groups. Thereafter, there was a steady increase in the prevalence of autonomic dysfunction reaching a peak prevalence of about 50% after 60 years of age in both the groups.

Figure 1 shows the results in relation to the duration of diabetes. In the 0-5 years duration group, 28.2% of Type 2 diabetes mellitus and 16.6% of FCPD patients had evidence of disordered autonomic function and these figures increased to 56.2% and 60% respectively, in the 16-20 years duration of diabetes. Logistic regression analysis, showed that only peripheral neuropathy was associated with autonomic dysfunction in Type 2 diabetes mellitus patients.
Gastrointestinal disorders:

Although gastrointestinal symptoms are not generally regarded to be major causes of morbidity in diabetic patients, 76% of diabetic patients evaluated at a referral centre had gastrointestinal symptoms (22). The gastrointestinal manifestations of diabetic autonomic neuropathy are diverse.

Esophageal Atony:

Esophageal immotility is well recognized; but symptoms such as inability to swallow (dysphagia), retrosternal discomfort and heart burn are uncommon (23). Manometry shows the absence of normal inter-digestive motor cycles in the stomach with astral hypermobility after indigestion of a solid meal (24). Recently developed radio-nucleotide diagnostic techniques are more sensitive and less invasive than manometry and may reveal a greater prevalence of esophageal motor dysfunction (25).

Gastroparesis Diabeticorum:

Diabetic autonomic neuropathy can impair gastric acid secretion and gastrointestinal motility. Impairment of gastric acid secretion may be due to vagal damage. This reduction in acid secretion leads to elevation of gastrin and hence stimulate proliferation of enterochromaffin cells to form “gastric carcinoid”.

This presents with gastric polyps and bleeding from the gastrointestinal tract and causes dyspepsia. This condition has been referred to as “diabetic pseudogastrinoma syndrome” (26). When gastric dysmotility is present, the patient may be anorexic and may experience vague upper abdominal fullness soon after eating, vomiting and early satiety. The patient may have frequent hypoglycemic episodes that makes diabetes control more difficult and lead to weight loss.

Gastric emptying can be assessed either by the standard method of barium meal radiography or by the more sensitive radio nuclide techniques (25). Furthermore, gastroduodenoscopy should be performed to exclude pyloric obstruction or other mechanical causes of obstruction.

Treatment should stress improvement of glycemic control and correction of other metabolic abnormalities. It also includes dietary modification (small, low fat and/or liquid meals), gastric suction, metoclopramide, domperidone, cisapride, bethanechol or antibiotic erythromycin. In some severe cases, jejunostomy may be needed to provide for feeding and resting the stomach. If the symptoms remain, surgery can be performed and best operation is surgical drainage using a Roux-en- Y-gastrectomy.
Colonic Atony and Diabetic Constipation / Diarrhoea syndromes:

Constipation is the most frequent gastrointestinal symptom in diabetic autonomic neuropathy, occurring in >60% of patients (25). It may be associated with atony of the large bowel and rectum and sometimes with megacolon (23). Other patients suffer from diabetic diarrhoea and some have alternating bouts of constipation and diarrhoea (25).

The symptoms of diabetic diarrhoea are characteristic, with intermittent episodes lasting from hours to days. The patient may have nocturnal diarrhoea and fecal incontinence, expelling more than 300g of stool (25) and may have as many as 20-30 bowel movements in 24 hours (23,25). Diarrhoea may result from intestinal hypermotility due to diminished sympathetic inhibition, hypomotility with bacterial overgrowth, pancreatic insufficiency steatorrhoea with a mucosal histologic pattern ("diabetic sprue") or bile salt malabsorption (24). Therapy may require polypharmacy to achieve relief. Codiene phosphate and loperamide should be avoided (24). If acute and severe, fluids and electrolytes should be prescribed. The first line should be to drive the bowel, eg. with propulsid. This is better than metaclopramide since it targets the large intestine. Bacterial overgrowth can be treated with a 3 week course of metronidazole. The intestinal disorder together with its treatment can raise blood glucose levels, therefore close monitoring should be enforced.

UROGENITAL SYSTEM DISORDERS

Neurogenic bladder:

Autonomic neuropathy affecting the sacral nerves causes bladder dysfunction. Bladder function tests are commonly abnormal in neuropathic diabetic patients but are relatively rare. In diabetic autonomic neuropathy, the motor function of the bladder is unimpaired, but afferent fibre damage results in diminished bladder sensation. Damage to parasympathetic innervation results in decreased tone and weakness of the detrusor, and loss of sympathetic innervation, of the internal urethral sphincter and the trigone causes sphincter dysfunction (25). The urinary bladder can be enlarged to more than three times its normal size. Patients are seen with bladders filled to their umbilicus, yet they feel no discomfort. Consequently, dribbling and overflow incontinence are common complaints and there is a predisposition to recurrent urinary tract infections.

The principles of treatment are to compensate for deficient bladder sensation and thus prevent the development of a
high residual bladder volume. The patient should be told to void every 3 hours during the day time; straining and suprapubic pressure may be needed. When more severe symptoms are present, more active treatment is required. Prazosin, an α-adrenoceptor blocker, may help by reducing urethral resistance. However one should be cautious of producing postural hypotension.

Sexual Dysfunction:

The prevalence of sexual dysfunction is about 50% in diabetic males and about 30% in women (25). Neuropathy can produce loss of penile erection or retrograde ejaculation or both in diabetic men. Retrograde ejaculation is caused by damage of efferent sympathetic innervation. Lack of spermatozoa in the semen and presence of motile sperm in a postcoital sperm of urine confirms the diagnosis (23).

Neurogenic erectile impotence is the most common form of organic sexual dysfunction in diabetic men, but impotence may have causes other than autonomic neuropathy. Impotence due to autonomic neuropathy has a gradual onset with progression to complete impotence over a period of 6 months to 2 years (23). Organic impotence can be confirmed by the documentation of nocturnal penile tumescence (NPT) and erection during rapid eye movements (REM) sleep. The absence of erections during REM with polysomnographic study sleep would confirm organic impotence.

Penile vascular insufficiency has been reported in certain diabetic impotent patients (23) and direct measurement of penile blood pressure with a doppler monitor can be done. These vascular insufficiency cases might be surgically correctable.

Sildenafil (Viagra) is a cGMP type 5 phosphodiesterase inhibitor that enhances blood flow to the corpora cavernosa with sexual stimulation. Before it is prescribed, it is important to exclude ischaemic heart disease. It is absolutely contraindicated in patients being treated with nitroglycerine or other nitrates-containing drugs. Direct injection of prostacyclin (27) into the corpus cavernosum will induce satisfactory erections. Also surgical implantation of a penile prosthesis may be appropriate for some patients.

Sweating disturbances:

Diabetic autonomic sudomotor dysfunction can be manifested by distal anhidrosis (diminished or absent sweating) following damage to sympathetic nerves of sweat glands. The anhidrosis usually has a patchy distribution over the lower extremity that diminishes thermoregulatory reserve and in severe
cases, may involve the lower trunk and arms. Loss of lower body sweating can lead to dry, brittle skin that cracks easily and predisposes to ulcer formation. Impaired sweating can be evaluated using simple starch, iodine or more sophisticated measurement of iontophoresis and by electromyographic evaluation of small nerve fibre function. Quantitative sudomotor axon reflex test (QSART), sweat beads and thermoregulatory control are the tests useful in evaluating sweat gland function.

Gustatory sweating is an uncommon symptom of sudomotor dysfunction and it occurs within seconds of eating a particular food (23). There is no current medication available for this problem, but some people benefit from a scopalamine patch behind the ear.

**Hypoglycemia unawareness:**

Blood glucose concentration is normally maintained during starvation by an asymptomatic parasympathetic response, followed by a sympathetic response for short-term glucose counter-regulation. The release of catecholamines alerts the patient to take required measures to prevent coma due to low blood glucose. The absence of warning signs of impending neuroglycopenia is known as “hypoglycemic unawareness”. The failure of glucose counter-regulation can be confirmed by the absence of glucagon and epinephrine responses to hypoglycemia induced by a standard controlled dose of insulin.

Premature mortality is not increased in patients whose sole manifestation of autonomic neuropathy is asymptomatic diminution of heart rate variability and over 90% remain alive after 10 years. However, those with symptomatic autonomic neuropathy have a worse prognosis, with a 10 year mortality rates of nearly 30%. Patients with postural hypotension have the highest mortality. In the early stage rapid improvement of glycemic control, reverses the autonomic nerve function (28). The Diabetes Control and Complications Trial (DCCT) (29) also demonstrated that intensive treatment group, showed improvement in autonomic nervous system function, confirming the importance of hyperglycemia in the pathogenesis of autonomic dysfunction.

**References**


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