

Human Immunodeficiency Virus Infection and Cardiac Autonomic Neuropathy

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Abstract—Human Immunodeficiency Virus is known to affect almost all organ systems in the body. In addition to central nervous system it also affects the autonomic nervous system. Autonomic nervous dysfunction has been known to severely affect the quality of life in human immunodeficiency virus positive patients. It is known to have caused fatal consequences in late stages of the disease in patients who go in for invasive diagnostic or therapeutic procedures. The aim of this review is to determine the incidence, clinical significance and frequency of cardiac autonomic neuropathy in patients human immunodeficiency virus infection

Keywords—Autonomic nervous system, autonomic nervous dysfunction, cardiac autonomic dysfunction, human immunodeficiency virus.

I. INTRODUCTION

AUTONOMIC dysfunction is more common and frequently occurs with greater severity in patients with human immunodeficiency virus infection (HIV) and is present in the early stages of HIV infection and progressive during the illness [1]. Syncope, presyncope, decreased sweating, diarrhea, bladder dysfunction and impotence are the early clinical signs of autonomic dysfunction in HIV infected patients. Subclinical autonomic neuropathy has been found in up to 50% of HIV infected patients but various studies have reported prevalence of autonomic nervous system dysfunction from 5% to 77% [2].

II. AUTONOMIC NERVOUS SYSTEM

The “Autonomic” nervous system (ANS) is a part of nervous system that is responsible for homeostasis. Except for skeletal muscle which gets its innervations from the somatomotor nervous system, innervations to all other organs are supplied by ANS. ANS may be defined as the part regulating all those bodily processes which are not under voluntary or volitional control [3]-[5].

The parts of the central and peripheral nervous system are included in ANS. The peripheral nervous system is concerned with innervation of viscera, glands, blood vessels and non-striated muscles. It is intimately responsive to changes in the somatic activities of body, and while its connections with

somatic elements are not always clear in anatomical terms, the physiological evidence of visceral reflex activities stimulated by somatic events are abundant [6], [7].

Probably the most remarkable feature of the ANS is the location of major part of it being outside the cerebrospinal axis, in proximity to the structures that it innervates. In somatic neuromuscular system, there is single motor neuron which bridges the gap between central nervous system and the effector organ but in autonomic nervous system there are two motor neurons, preganglionic and postganglionic fibres. The autonomic out flow is regulated by centers in brain stem. Hypothalamus is the most important cell station which finally controls visceral and other autonomic activities. Hypothalamus is influenced by different parts of brain like hippocampus, amygdala, cingulate gyri and prefrontal cortex and also from periphery through baroreceptors and chemoreceptors, receptors in skin, muscle and viscera [8].

The ANS has two major and anatomically distinct divisions: The sympathetic and parasympathetic nervous systems. These two systems are antagonistic of each other in their effects on the effector organs. The preganglionic efferent fibers of parasympathetic nervous systems emerge through certain cranial and sacral spinal nerves and constitute the craniosacral outflow. On the other hand, preganglionic efferent fibers of the sympathetic nervous system emerge through thoracic and upper lumbar spinal nerves and constitute the thoracolumbar outflow. The cell bodies of the preganglionic neurons are located in the intermediolateral column of spinal cord and in motor nuclei of some cranial nerves. Their axons traverse corresponding to cranial and spinal nerves to enter ganglia, where they synapse with dendrite or somata of secondary neurons. One preganglionic neuron synapses with many postganglionic neurons, a circumstance which is associated with wide distribution of many autonomic effects. This disproportion of preganglionic to postganglionic is greater in sympathetic than in parasympathetic nervous system [9].

The cell bodies of postganglionic neurons in the parasympathetic system are situated peripherally. The cell bodies of postganglionic neurons in sympathetic trunk are in ganglia in peripheral plexuses, almost nearer to spinal cord that the organ innervated. The fibers which convey the message to ganglia are finely medullated but fibers to effector organ are non-medullated. The physiological functions like blood flow, blood pressure, heart rate, airflow in the respiratory tree, motility of gastrointestinal tract, contraction of urinary bladder, secretions from glands, changes in diameter of pupils, temperature of body and sexual functions are regulated and coordinated by the ANS. Physiologically,

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parasympathetic reactions are generally localized, whereas sympathetic reactions are mass responses. Passage of nervous impulses along all preganglionic fibers, parasympathetic, postganglionic fibers are associated with liberation of acetylcholine in the region of terminals. The above types of nerves are called cholinergic and adrenergic respectively [10].

TABLE I
AUTONOMIC EFFECTS ON ORGANS OF THE BODY [11]

Organ	Effect of sympathetic stimulation	Effect of parasympathetic stimulation
EYE		
Pupil	Dilated	Constricted
Ciliary muscle	Slight relaxation (far vision)	Constricted (near vision)
GLANDS		
Lacrimal	Vasoconstriction and slight secretions	Stimulation of copious secretion
Parotid		
Submandibular		
Gastric, Pancreatic		
APOCRINE GLANDS	Thick, odoriferous secretion	None
BLOOD VESSELS	Most often constricted	Most often little or no effect
HEART		
Muscle	Increased rate and force of contraction	Slowed rate and decreased force of contraction
Coronary artery	Dilated (beta 2): constricted (alpha)	Dilated
BLADDER		
Detrusor	Relaxed	Constricted
Trigone	Constricted	Relaxed
GUT		
Lumen	Decreased peristalsis and tone	Increased peristalsis and tone
Sphincter	Increased tone	Relax
LUNGS		
Bronchi	Dilated	Constricted

III. AUTONOMIC DYSFUNCTION

A. Pathogenesis of the Autonomic Dysfunction of HIV Infection

After initial exposure HIV enters the brain, probably through infected monocytes and lymphocytes which cross the blood brain barrier [13].

B. Crossing the Blood Brain Barrier

The HIV surface glycoprotein gp160, contains two components, gp120 and gp41. The gp160 allows the virus to attach to host cell receptors like the CD4 receptor and CXCR4 or CCR5 co-receptor and become internalized. The CCR5 is the main co-receptor for macrophage- tropic HIV-1 strains and is the predominant strain found in the central nervous system. Following infection with HIV, CCR5-bearing macrophages cause activation of markers such as CD16 and carry HIV into the brain through a 'Trojan horse' mechanism. The brain's specialized and native immune microglial cells become infected through contact with these trafficking macrophages [14].

TABLE II
CAUSES OF AUTONOMIC DYSFUNCTION [12]

Etiological Category	Selected Etiologies
Structural Disorders	
Developmental structural disorders	Arnold-Chiari malformation Syringomyelia Normal pressure hydrocephalus
Hereditary and Degenerative Disorders	
Movement disorders	Multiple system atrophy
Degenerative motor, sensory and autonomic disorders	Riley-Day syndrome Pure autonomic failure
Inherited muscle, neuromuscular and neuronal disorders	Amyloidosis
Acquired Metabolic and Nutritional Disorders	
Endogenous metabolic disorders	Diabetes mellitus
Nutritional deficiencies and syndromes associated with alcoholism	Wernicke's encephalopathy
Infectious Disorders	
Viral infections	Poliomyelitis
Transmissible spongiform encephalopathy	Fatal familial insomnia
HIV and AIDS	HIV associated neuropathy HIV related Guillain Barre syndrome Vertebrobasilar ischemia
Neurovascular Disorders	
Neoplastic Disorders	
Primary neurological tumours	Brain stem glioma
Demyelinating Disorders	
Demyelinating disorders of central nervous system	Multiple sclerosis with bladder dysfunction
Demyelinating disorders of peripheral nervous system	Guillain Barre syndrome
Autoimmune and inflammatory Disorders	
Traumatic Disorders	Lambert Eaton myasthenia gravis syndrome Spinal cord: Blunt or penetrating trauma
Epilepsy	Temporal/Limbic seizures
Headache and facial pain	Cluster headache
Drug induced and iatrogenic neurological Disorders	Drugs: Chemotherapeutic agents

TABLE III
DYSAUTONOMIA SYMPTOMS [1]

Cardiovascular symptoms	Postural hypotension, Vertigo, Syncope, Palpitations
Upper Gastrointestinal symptoms	Dysphagia, Nausea / emesis, Early satiety, gastric fullness or bloating diarrhoea, or constipation
Lower Gastrointestinal symptoms	Involuntary loss of stool, feeling of incomplete fecal evacuation
Urogenital symptoms	Dysuria, involuntary loss of urine, prolonged dribbling, feeling of incomplete
Others	Increased sensitivity to light, hypo or hyperhidrosis or gustatory sweating

C. Mechanism of Neuronal Injury

Although neurons are not infected by HIV, they can be injured via indirect mechanisms

1. Neurotoxins from infected microglial cells (arachidonic acid metabolites and platelet activating factor)
2. gp120- mediated neuronal growth factor blockade or killing
3. Neurotoxicity by HIV tat or viral regulatory components.

All or one of these mechanisms may cause cytotoxic effects in neurons and/or oligodendrocytes. The secretory products from HIV-infected cells cause alteration in neuronal viability, damage to myelin and stimulate neurotransmitters causing neuronal dysfunction [15], [16].

Neuroinflammation is characterized by several pro-inflammatory events including the release of pro-inflammatory cytokines such as IL-1 β , -6, TNF- α , and chemokines that drive this process. IL-1 β leads to NF-kB dependent transcription of pro-inflammatory cytokines including TNF- α , IL-6 and interferon. Tat stimulates cytokine/chemokine networks in monocytes and macrophages. HIV-1 encoded viral protein R (Vpr) has been shown to modulate several chemokines at the transcriptional level by regulating NF-kB-mediated transcription [17]-[20].

Surface glycoprotein gpl20 may antagonize normal vasoactive intestinal peptide (VIP-ergic) function in brain or be directly toxic to neurons. Studies show that gpl20 can induce neuronal toxicity by the N-methyl D-aspartate receptor activation and consequent influx of calcium into the cell and neurons containing nitric oxide synthetase cause secondary synthesis of nitric oxide [21].

The tissue damaged by the cytokines then becomes secondarily infected. Moreover, as HIV-1 disease advances and there is a reduction in CD4 + cells there is a selection towards these infected microglial cells that further infect the brain. Pathological outcomes of HIV-1 infection in brain tissue include neuronal loss, reactive astrogliosis, and myelin damage. Neuronal loss is strongly associated with axonal and dendritic damage in the cortex and subcortex of affected individuals [22]. The cytokines that are released by macrophage cells during an attempt to control infection affect the peripheral nerves [23].

IV. CARDIAC AUTONOMIC DYSFUNCTION

In 1999, Rogstad et al. studied autonomic function in HIV positive patients in different stages of infection and in controls. 25 patients with seven asymptomatic HIV, eight AIDS related complex, 10 AIDS patients and 25 controls were studied. Autonomic function was assessed; CD4 count was correlated with number of abnormal test results. At least one abnormal test of autonomic function was observed in 21 patients when compared with control ($p < 0.0001$). Significant differences in supine heart rate ($p < 0.001$), valsalva ratio ($p = 0.05$), cold face test ($p = 0.05$) and mental stress ($p = 0.051$), were present between AIDS patients and controls. The CD4 count was less than $300 \times 10^6/\mu\text{L}$ in all patients with four abnormal tests of heart rate variations. In this study irrespective of CD4 count there was evidence of substantial autonomic dysfunction in AIDS patients compared with controls and mild abnormalities in the majority of HIV infected patients [24].

Heart rate variability (HRV) in HIV positive individuals was investigated by Mittal et al. They conducted the study to find out if HRV is depressed in HIV positive individuals without AIDS. They studied prospectively HRV by spectral analysis of short-term ECG monitoring in 21 HIV positive (33 ± 11 years) and in 18 healthy volunteers (31 ± 9 years). All these individuals did not have any evidence of AIDS. Mean CD4 lymphocyte count was $426 \pm 166/\mu\text{L}$. The ejection fraction (EF) of HIV patients was $62.4 \pm 6.4\%$. They found that the total power of HRV was reduced significantly in HIV-positive

individuals ($p < 0.00001$) in early stages of infection as well without any clinical evidence of autonomic dysfunction [25].

In one of the first studies in Africa in 2002, Nzubontane et al. investigated the effects of HIV on cardiac autonomic function. They performed standard heart-rate and blood pressure tests on 75 consecutive consenting. 54 patients proved to be HIV-infected with 30 having progressed to AIDS. Cardiovascular autonomic dysfunction was present in eight (28%) patients with AIDS and in one (4%) HIV-positive patient without AIDS; no HIV-negative individuals had abnormal results. If borderline results are included, over 80% of HIV-positive patients had cardiovascular autonomic dysfunction [26].

In 1997, Becker et al. examined the degree, pattern, and natural history of cardiac autonomic nervous dysfunction in patients infected with HIV. They found that the AIDS patients demonstrated reduced HRV in 14 parameters (93.3%) compared with healthy subjects ($P < 0.017$) whereas pre-AIDS patients as a group did not exhibit any HRV parameters to be significantly different from healthy controls ($P > 0.017$). They concluded that the cardiac autonomic nervous dysfunction although not significant in pre-AIDS patients but is severe in AIDS patients and proceeds with HIV disease progression, although its individual course is slow [2].

In a controlled trial in 1991, Ruttimann S. et al. conducted tests to determine frequency and severity of autonomic neuropathy in patients infected with the HIV. The autonomic neuropathy was graded with a scoring system in a study of twenty five HIV-seropositive patients and ten seronegative controls in HIV risk groups by means of five cardiovascular tests and the overall autonomic test score varied between patients and controls. The tests score was higher in patients with advanced disease than in patients with earlier HIV disease. Of the patients, 60% had findings of autonomic dysfunction. The data demonstrates a high prevalence of autonomic neuropathy in HIV-infected patients and advanced HIV disease is associated with more severe involvement than earlier disease states [27].

Freeman et al. studied autonomic function in 26 patients of HIV infections where 18 patients with AIDS and eight with ARC to 22 controls. There was a significant decline in autonomic function across the groups. The signs of HIV-associated nervous system disease strongly correlated with autonomic dysfunction. Significant differences were observed across groups in tests like heart rate variation, changes in mean arterial blood pressure from fall to tilting and variations in blood pressure to isometric exercise. The autonomic dysfunction was found more frequently with greater severity in patients with AIDS; however, it was present in the early stages of HIV infection and progressed during the course of illness [28].

Orthostatic hypotension as a result of generalized ANS dysfunction was investigated by Cohen et al. in HIV positive patients. They used an ANS testing battery to determine if generalized ANS dysfunction was present in five HIV positive patients presenting with severe orthostatic hypotension. All five patients had abnormal ANS testing, which demonstrated

both sympathetic and parasympathetic defects, i.e., generalized ANS dysfunction. Treatment with fludrocortisone effectively reversed the orthostatic hypotension in four of the five patients. The orthostatic hypotension was transient in these four patients. They stated that it is important to recognize that orthostatic hypotension may be the result of generalized ANS dysfunction in HIV-positive patients and it can be effectively treated [29].

V. DIAGNOSIS OF CARDIAC AUTONOMIC NEUROPATHY

Many tests for testing autonomic functions have been described. However the following are standardized and well accepted.

1. Heart rate variation to deep breathing.
2. Valsalva ratio
3. Heart rate response to standing
4. Systolic fall in blood pressure to standing
5. Diastolic rise in blood pressure to sustained hand grip.

A. Heart Rate Variation Deep Breathing

During deep inspiration and expiration, the heart rate varies which is called sinus arrhythmia. Sinus arrhythmia is a result of several circulatory reflexes. First, when blood pressure rises and falls during each cycle of respiration, the baroreceptors are alternatively stimulated and depressed, causing reflex slowing and speeding of heart. Second, during each respiratory cycle, the negative intra-pleural pressure increases and decreases effective pressure in veins of chest. This elicits a waxing and waning Bainbridge reflex which alters heart rate.

Procedure: The patient is asked to breathe normally and long lead II on electrocardiography (ECG) is recorded. The patient is then asked to take deep breath, after about one minute a long lead II on ECG is recorded.

Interpretation: All these reflexes are blunted in autonomic neuropathy. The difference in heart rate of greater than 15 beats per minute is normal and a difference of less than 10 beats per minute is abnormal. A difference of heart rate between 11 and 15 beats is borderline.

B. Heart-Rate Response to Valsalva Maneuver

When a person performs Valsalva maneuver, a sharp reduction in venous return and cardiac output; this causes baroreceptors to produce less impulses and reflex tachycardia and peripheral vasoconstriction occurs with releases of intrathoracic pressure, the venous return, stroke volume and blood pressure return to normal.

Procedure: A lead II recording is done on ECG. The patient is then asked to breathe through into a mouth piece connected to a modified sphygmomanometer and holding it at a pressure of 40 mm Hg for 15 seconds while a continuous lead II ECG is recorded.

Interpretation: In parasympathetic dysfunction during release phase, bradycardia does not occur. This is utilized in calculating Valsalva ratio, the longest R-R interval after maneuver is divided by shortest R-R interval during maneuver. A ratio greater than 1.21 is normal 1.11 to 1.20 is borderline and less than 1.10 abnormal [30].

C. Heart Rate Response to Standing

Upon standing, systemic pooling of blood in venous system occurs. This leads to reduction in cardiac output, decreased baroreceptor discharge and consequently vasomotor center is stimulated causing tachycardia.

Procedure: The patient is asked to lie supine and a lead II recording is done on ECG. The patient is asked to stand up and the recording continued.

Interpretation: Heart rate increases until it reaches a maximum at about fifteenth beat, the normal increase being in range of 11 to 29 beats per minute. The ratio of R-R intervals corresponding to thirtieth and fifteenth heart beat is known as 30:15 ratio. The ratio of 1 or less is considered abnormal [31].

D. Systolic Fall in Blood Pressure on Standing

Normally as one stands, there is pooling of blood in distensible lower limb veins due to pull of gravity below heart, decreasing venous return. This triggers a series of physiologic adjustments designed to maintain adequate perfusion. Stimulated baroreceptors provoke autonomic nervous activity, which results in an increase in peripheral arterial and venous constriction, heart rate and myocardial contraction.

Procedure: The patient's blood pressure is measured when the patient is in supine position and again when he is standing up.

Interpretation: A systolic pressure fall of 30 mm of Hg at end of three minutes indicates abnormal response of sympathetic system [32].

E. Diastolic Rise of Blood Pressure in Response to Sustained Hand Grip (Isometric Contraction)

During sustained isometric contraction of a group of muscles, an increase in heart rate, arterial blood pressure and cardiac output occurs. The cardiovascular responses are mediated partly by central contracting muscles that activate small fibers in afferent limb arc. This results in increased sympatho-adrenal discharge.

Procedure: The patient is asked to maintain sustained voluntary hand grip as long as possible. Blood pressure is recorded before and during the procedure.

Interpretation: An increase in diastolic pressure of more than 16 mmHg is normal and less than 10mm of Hg is abnormal. This is also a test for sympathetic system. 11 mm Hg to 16 mm Hg is border line [33].

VI. MANAGEMENT OF AUTONOMIC NEUROPATHY

The most troublesome effect of the autonomic dysfunction is orthostatic hypotension. Management includes patient education to avoid fall in blood pressure. Patients should be made aware of hypotensive effects of certain drugs, large meals, environmental temperature increases and physical activities [34], [35].

A. Physical Measures

These patients are advised not to suddenly arise from beds; instead, they should first exercise the legs by crossing them and lowering the head in a stooped position, bending forward

and placing a foot on a chair or squatting. They should avoid straining during micturation and defecation. A snug elastic abdomen binder and elastic stocking are often helpful.

TABLE IV
SCORING FOR CARDIAC AUTONOMIC DYSFUNCTION

Test	Normal	Abnormal	
		Borderline	Definite
Systolic fall of blood pressure on standing	Less than 10 mm of Hg	11-29 mm of Hg	More than 30 mm of Hg
Expiratory/Inspiratory ratio	More than 15 beats per minute	11-15 beats per minute	Less than 10 beats per minute
Valsalva ratio	More than 1.21	1.11 - 1.20	Less than 1.10
Heart rate response on standing	More than 1.04	1.01 - 1.03	Less than 1.00
Blood pressure to sustained hand grip	More than 16 mm of Hg	11- 15 mm of Hg	Less than 10 mm of Hg

To avoid postprandial hypotension, patients should eat smaller, low carbohydrate meals more frequently. Elevation of head end of bed 15 to 30 cm at night is also advocated, which avoids supine hypertension and decreases nocturnal natriuresis and volume depletion [36].

B. Drugs

- Diuretics: If patients are on diuretics they should be advised to stop if there are no contraindications.
- Fludrocortisone: It increases the blood volume and it has effect on noradrenaline release from sympathetic terminals and sensitizing the vascular receptors to vasopressor amines. It is recommended at dosage of 0.1 mg orally qid this is increased slowly in 0.1 mg increments at 1 to 2 week interval.
- Vasoconstricting sympathomimetic agents-Ephedrine, methylphenidate, phenylpropanolamine or phenylephrine, midodrine may be used.
- Metoclopramide which is a dopamine antagonist which blocks the vasodilator effect of dopamine and caffeine which prevents postprandial hypotension. Somatostatin also prevents the postprandial hypotension. Recombinant erythropoietin alpha corrects anemia which is usually present and increases blood pressure and orthostatic tolerance [37], [38].

C. Bladder Disturbances

In bladder obstruction due to increased tone, adrenergic blockers are advocated. Atonic bladder is treated with carbachol or bethanechol. Urinary tract infections should be treated with appropriate antibiotics. Other surgical methods are bladder neck resection; sphincterostomy, urethral catheterization and suprapubic cystostomy. [39].

D. Gastrointestinal Disturbances

Gastric atony and reflux esophagitis may be treated with metoclopramide; diarrhea with bowel binding agents like, loperamide, codeine and diphenoxylate. For constipation increased roughage in diet is advised.

Sweating abnormalities:

1. For hyperhidrosis -- Propanthelene

2. For anhidrosis -- Petroleum jelly

Impotence: Treatment includes

1. Local papaverine with or without phentolamine.
2. Surgical implants.

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