Case Discussion in Medicine

The Autonomic Nervous System (ANS) : An appraisal and revisit

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The autonomic nervous system has a cardinal role in maintaining the internal homeostasis of the body. Yet, till today it somehow remains as a neglected or less understood aspect of neurology. Disturbances of autonomic nervous system may have protean manifestations and with recent advancements pathogenesis of many diseases have been linked to autonomic dysfunction. In this review, the authors intend to discuss about the basic anatomy and physiology of the autonomic nervous system and also a brief highlight of clinical examination as well as concerned laboratory investigations to detect autonomic dysfunction.

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Key words **: Autonomic nervous system, examination, laboratory investigations.**

The autonomic nervous system has remained a Cinderella specialty. The motor and sensory system examinations are carefully drilled into every medical student ever since they enter the clinical curriculum and is discussed and recapitulated throughout their clinical career. Unfortunately, the poor cousin, the autonomic nervous system and its relevant examination remains a nuance even to post graduate neurology trainees and even to established practitioners of neurology globally. The potential explanation for this may arise from the seemingly complex network, architecture and organisation of the autonomic nervous system compared to the rather straight forward layout of the peripheral motor and sensory pathways; these start to get complex only when they enter the cerebrum. For this same reason, the cerebral association pathways have been traditionally inadequately approached although with work in the dementias, epilepsies and movement disorders and the modern imaging, these are also slowly getting rectified[1].

Case Scenario :

A 53-year-old gentleman without any comorbidity, on mixed diet was admitted in the Neurology ward of a tertiary care hospital with chief complaints of slowing of activities for 3 years followed by urinary urgency and incontinence as well as recurrent falls for last 1 year.

Editor's Comment :

- **Autonomic nervous system is an integral part of nervous system which is necessary to maintain the internal milieu.**
- **The paucity of specific history, examination and limited resources have hindered the exploration of the autonomic nervous system compared to other aspects of neurology.**
- **With advanced research and growing resources, multiple disease pathogenesis have been linked to autonomic dysfunction.**
- **The autonomic nervous system may be incorporated into the curriculum of medical students with equal importance as compared to motor and sensory system of human neurology, to necessitate better understanding of the subject and improved patient care.**

History of present illness :

The patient experienced a gradually progressive slowing of daily activities over the last 3 years. His wife first noticed that his walking speed had a significant decline and he used to take a lot more time than usual to stand up from sitting position and even turning on bed. He was also experiencing undue stiffness of his limbs and that hampered his daily activities. One year back, he started to experience urinary urgency followed by incontinence. He used to suffer from dizziness when standing up from supine position and had a few episodes of pre-syncope. He has been suffering from erectile dysfunction for the last 5 years. He developed mild tremor of both hands on activities but not at rest. Gradually, he became

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stooped with history of recurrent falls, without any loss of consciousness, seizures. His wife has recently noted that his speech has become slurred and he also had two episodes of choking sensation while swallowing food. No history of forgetfulness or psychotic outbreaks were obtained.

No history of addiction or any significant family history was obtained. He has received a combination of levodopa/carbidopa over the last 3 years, with minimal improvement.

Clinical Examination

- Conscious, alert and oriented
- Normal higher function/cognition
- BP= 140/80 mmHg (supine), 110/70 mmHg (standing); Pulse rate= 86/min (regular)
- Masked facies
- Hypophonia
- No signs of meningeal irritation
- Cranial nerves
  - No restriction of extraocular movements, occasional square-wave jerks, hypometric saccades with broken pursuit; bilateral gaze evoked nystagmus.
  - Brisk jaw jerk, gag reflex intact
  - Mixed dysarthria
  - Other cranial nerves were normal
- Motor system: Symmetric rigidity in all 4 limbs with normal bulk and power. Axial rigidity markedly present. Bradykinesia in all 4 limbs with a postural/action tremor on distal bilateral upper limbs.
- Deep tendon reflexes 2+
- Bilateral flexor plantar
- Sensory system: normal
- Mild impairment of coordination on both sides
- Broad based gait with short shuffling steps, freezing of gait, stooped posture, reduced bilateral arm swing.
- Retropulsion and lateropulsion test was positive.

How to approach the case from history?

- Slowing of activities and walking speed suggestive of bradykinesia (differential of bradykinesia such as depression, hypothyroid unlikely)
- Stiffness of limbs suggestive of rigidity, probably due to extrapyramidal system involvement.
- Tremor on activity suggestive of action tremor
- **Urinary urgency and incontinence, pre-syncope, dizziness, erectile dysfunction suggestive of significant autonomic nervous system.**
- Recurrent falls suggestive of postural instability
- Slurring of speech is suggestive of dysarthria and choking may be due to dysphagia.

How to approach the case from examination?

- Postural drop in blood pressure suggestive of orthostatic hypotension.
- No supranuclear gaze palsy, other ocular findings suggestive of both extrapyramidal and cerebellar involvement.
- Possibility of pseudobulbar palsy due to brisk jaw jerk, likely UMN type dysphagia and mixed dysarthria.
- Symmetric bradykinesia with appendicular and axial rigidity suggestive of atypical parkinsonian features.
- Incoordination may suggest cerebellar involvement.

Analysis of the case:

- Bradykinesia, rigidity and postural instability are suggestive of parkinsonian features.
- Chronic progression is suggestive of probable degenerative etiology.
- Absence of rest tremor, lack of asymmetry, **early and significant autonomic dysfunction** and lack of levodopa response suggests atypical parkinsonism.
- **Involvement of the autonomic system in a background of atypical parkinsonism may point towards the diagnosis of Multisystem atrophy (MSA), probably MSA-P (Multisystem atrophy with predominant parkinsonism)**

Discussion

The autonomic nervous system does not lend itself to individual pathway delineation akin to an electrical circuit but rather assesses the complex interplay of the sympathetic and parasympathetic systems (Figs 1,2) which are essentially controlled by adrenaline, noradrenaline and acetylcholine (and the various receptor types-Table 1) and the pre and post ganglionic ganglia neurochemicals and receptor subtypes and nerve endings and in the central connexions and influences from higher cortical centres. From the history taking perspective patients also find it difficult to describe rather diffuse symptomatic presentations (Table 2) of dysfunction of the autonomic nervous system that makes localisation on history challenging[2].

The autonomic nervous system which essentially helps to maintain the internal milieu or homeostasis (Claude Bernard)[3,4] has important ramifications in the regulation of the cardiovascular system, gastrointestinal system, sudomotor system and the urogenital functions all of which are taken for granted as part of our everyday existence. Again, with dysfunctions in these various systems coming on gradually it becomes difficult to delineate from history

the impact of progressive dysfunctions in this system and are liable to be confused or confounded with motor system dysfunctions of which there is a significant overlap anyway[5]. Again, the autonomic nervous system dysfunctions are predominantly diagnosed and confirmed through lab tests which we have not utilised traditionally through lack of availability and resources. The degrees of assessment of the ANS tends to get more and more complex as one develops a deeper understanding of the domains of dysfunction[6].

We believe the knowledge of the physicians happens to be the main limiting factor and the lack of regular discussions of the autonomic nervous system as part of the general undergraduate and postgraduate medical discourse now deserves rectification. Certainly, in the post graduate neurology curriculum a practical and detailed approach to the autonomic nervous system assessment needs to be established with due emphasis akin to strokes, Parkinson's and epilepsies[7-9].

The perceived neglect of the autonomic nervous system has also stemmed from the interdisciplinary ramifications of diseases that ANS causes. The cardiologists, gastroenterologists, internal medicine colleagues, ophthalmologists, endocrinologists, pulmonologists, dermatologists and psychiatrists and all physicians who have prescribing responsibilities are stakeholders in the ANS as either the primary symptoms or drug side effects that these specialities deal with are often manifestations of the ANS dysfunction. This multispecialty stake holding status has resulted in one particular specialty or clinician failing to take complete ownership of assessment of the autonomic nervous system as it is perceived as a very complex and elaborate subspecialty. Hence in the West, practitioners of autonomic nervous system medicine tend to be restricted to a handful with elaborate ANS labs that satisfy the needs of anyone of the above-mentioned stakeholders in the field[10].

With diabetes casting it's wide net and its impact on the autonomic nervous system and a wide spectrum of medications that we are using in every specialty which have an impact on the sympathetic and parasympathetic pathways including the medications used by our psychiatric colleagues for modulation of cortical and limbic and frontal and parietal circuits there is a need for all of us to become more fluid in our understanding, diagnosis and our advice to patients and judicious use of corrective measures including general lifestyle advice which often entrains and modulates the autonomic nervous system dysfunctions to restore normality in our patients lives[12].

Use of pharmacotherapy carefully to identify offending medications that result in the autonomic nervous system disorders also becomes mandatory. Neuroimmunology has resulted in the identification of a large number of antibodies which operate at neuronal level or ganglion level resulting in transmission disturbances at the preganglionic and postganglionic nerve endings and more are likely to be identified with technological progress of bioassay techniques. This will lead to immunomodulatory therapy based on evidence.

Time has come when autonomic clubs need to be established by a spectrum of specialties including medical and surgical and not necessarily restricted to neurosciences which will lead to the benefit of our patients. This reflects the large number of specialities that the patients with diffuse ANS symptoms may land up with.

Anatomy and physiology :

A) History :

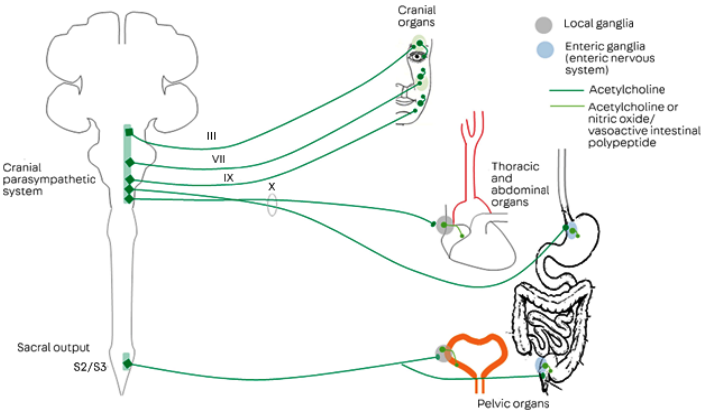

Fig 1 — Organisation of the Sympathetic nervous system

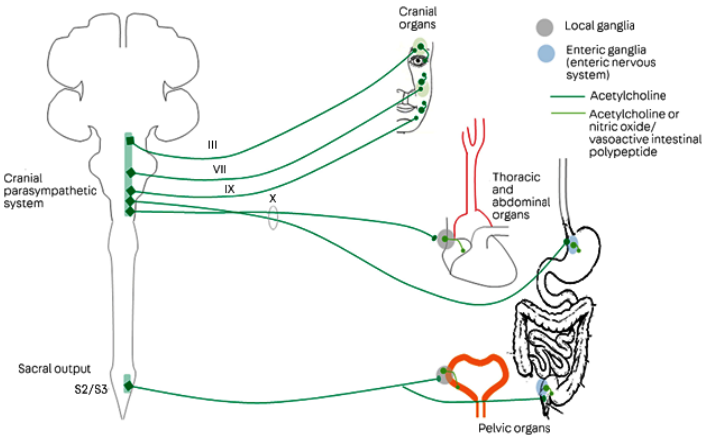

Fig 2 — Organisation of the parasympathetic nervous system

There is never a single clearly articulated localising symptom for ANS disorders that makes history taking a true exercise in deductive reasoning skills. As usual the onset, temporal course and profile and any aggravating or alleviating factors for any of the symptoms the patient describes, relationship to environmental temperature and postural changes, role of dietary supplements, over-the-counter medications and traditional remedies (homeopathic and ayurvedic) and the impact of the symptoms on the patient's quality of life needs to be deftly obtained. The intention here is to identify the syndromic dysautonomia resulting from involvement of the sympathetic, parasympathetic and enteric divisions. The sympathetic nervous system comprises noradrenergic, adrenergic and cholinergic systems in which the primary chemical messengers are norepinephrine, epinephrine and acetylcholine, respectively. Sympathetic noradrenergic and cholinergic neurons, which are non-myelinated and slowly conducting, derive from thoracolumbar segments of sympathetic ganglia. Sympathetic adrenergic neurons are myelinated and rapidly conduct and pass through the sympathetic ganglia without synapsing to innervate the adrenal medulla. Parasympathetic neurons arise from the brainstem or sacral spinal cord and being myelinated rapidly conduct and are cholinergic with their ganglia near to or embedded in their target organs.

The enteric neurons derived from neural crest cells are embedded in the lining of the gastro- intestinal tract. The myenteric plexus controlling gastrointestinal motility receives parasympathetic innervation from the vagus and sympathetic innervation from post ganglionic sympathetic neurons. The submucous plexus which provides secretomotor innervation receives parasympathetic innervation only[13].

Table 1— Effects of the sympathetic and parasympathetic nervous system on various target organs (with autonomic receptor subtypes in brackets)

Target	Sympathetic (Receptor)	Parasympathetic (Receptor)
Pupil	Dilation (α_1)	Constriction (M_3)
Ciliary muscle	NA	Accommodation (M_3)
Salivary and lacrimal glands	Inhibition (α_2?)	Stimulation (M_3, vasoactive intestinal polypeptide receptors)
Heart	Stimulation (β_1)	Inhibition (M_2)
Bronchi	Dilation (β_2)	Constriction (M_3)
Skeletal muscle vessels	Constriction (α_1) Dilation (β_2)	NA
Skin vessels	Constriction (α_1) Dilation?(nitric oxide?)	NA
Cranial and visceral vessels	Constriction (α_1)	Dilation(nitric oxide, vasoactive intestinal polypeptide)
Sweat glands	Stimulation (M_3)	NA
Gastrointestinal motility	Inhibition (β_2)	Contraction (M_3) Relaxation (nitric oxide, vasoactive intestinal polypeptide receptors)
Gastrointestinal secretion	Inhibition (α_2)	Gastric acid secretion (M_1); intestinal secretion (M_3, vasoactive intestinal polypeptide receptors)
Bladder detrusor	Inhibition (β_2, β_3)	Stimulation (M_3)
Bladder neck	Stimulation (α_1)	Inhibition (nitric oxide)
Rectal smooth muscle	Inhibition (β_2)	Stimulation (M_3)
Erectile tissue	Constriction (α_1)	Dilation (nitric oxide)
Vas deferens	Contraction (α_1)	NA

NA = not applicable.

Table 2 — Autonomic Symptoms and Signs

	Sympathetic			Parasympathetic	
Function	Noradrenergic	Adrenergic	Cholinergic	Cranial	Sacral
Decreased	Orthostatic hypotension, lack of tachycardia, Horner syndrome	Fatigue, hypoglycemia	Decreased sweating	Dry mouth, mydriasis, constipation	Urinary retention, maleerectilefailure
Increased	Palpitations, increased systolicbloodpressure, tachycardia, mydriasis, sweating, cold hands, salivation, piloerection	Palpitations, increased systolic blood pressure, tachycardia, mydriasis, pallor,coldhands,slowed gastrointestinal transit, anxiety, tachypnea, bronchial dilation, hyperglycemia	Increased sweating	Salivation, bradycardia, bronchial constriction, miosis, lacrimation	Nausea, urinary frequency, increased gastrointestinal transit

I. The sympathetic noradrenergic disorders present with symptoms of orthostatic hypotension (OH) with patients reporting dizziness, light-headedness, weakness, fatigue, dimness of vision and difficulty in thinking or maybe entirely asymptomatic. These symptoms are often worse during early morning hours (through relative dehydration), heat exposure, exercise and meals due to the redistribution of circulating blood volume and effects of vasodilators, diuretics and alpha blockers can unmask OH. Male ejaculatory failure, eyelid ptosis and lack of piloerection in response to cold are other symptoms. Sympathetic noradrenergic hyperactivity can cause palpitations, hypertension, tachycardia, pupil dilatation, cutaneous vasoconstriction. Intake of stimulant medications either over the counter or prescribed need to be scrutinised. Reduced adrenaline secretion from the adrenal medulla results in non-specific symptoms of fatigue while excess adrenaline production manifests as palpitations, pallor, dilated pupils and sweating[14].

II. Sympathetic cholinergic disorders: failure of the system results in loss of sweating, impairing thermoregulatory function as acetylcholine is the primary neuro chemical messenger at eccrine neuro effector junctions. Patients do not tolerate hot weather particularly when exercising and feel lightheaded and tired and prickly paraesthesia in hot environments. In absence of sweating

cutaneous flushing occurs and heat exhaustion and heat stroke may result. Compensatory hyperhidrosis may occur in body regions that retain sweat function. Medications including anticholinergic drugs, carbonic anhydrase inhibitors cause reduced sweating. Hyperhidrosis is a common side effect of opioids, SSRIs and SNRIs from sympathetic cholinergic hyperactivity[15].

III. Parasympathetic nervous system disorders: the cranial component dysfunction results in easily recognised dry mouth, dilated pupils, increase in heart rate, decreased heart rate variability and constipation. Failure of the sacral competent results in urinary bladder retention and male erectile failure. Parasympathetic overactivity manifests as increased salivation, slow heart rate, nausea and urinary frequency and urgency.

IV. Enteric nervous system disorders: nausea, bloating, early satiety, reflux, gastroparesis, constipation and colonic pseudo obstruction may result[16].

B) Autonomic physical examination

The examination is informed by an intelligently gathered autonomic history as above.

1) Orthostatic vital signs: measurement of blood pressure and heart rate while standing compared to baseline values obtained when seated and supine. The key diagnostic distinction is to identify neurogenic orthostatic hypotension and differentiate from dehydration, heart failure, deconditioning or vasodilator drugs.

2) Pupillomotor signs : pupillary size asymmetry dependent on sympathetic and parasympathetic denervation are more noticeable in the dim and bright light respectively and easily detectable in the clinic although formal pupillometry studies offer objective and follow-up pupil size measurements.

3) Sudomotor signs : dry skin is detected by palpation compared to normal skin. Focal hyperhidrosis is seen in the dark by shining a bright torch when the sweat droplets render the skin shiny.

4) Secretomotor signs : dry eyes and dry mouth in Sjogren's syndrome are well recognised

5) Vasomotor signs : facial flushing occurring during emotional arousal, menopause and hormonal disbalance, anticholinergic and antioestrogen medication use, carcinoid syndrome, polycythaemia vera or mastocytosis can be seen in photographs while bystanders will report facial pallor preceding neutrally mediated syncope. In Harlequin syndrome the sympathetically denervated pale and dry half of the face is the abnormal side and not the flushed side that shows compensatory overactivity. Distal arteriolar vasoconstriction manifests as cold feet and hands in patients with autonomic neuropathies and vasomotor instability leads to venous pooling resulting in red or purple erythema in the extremities[17].

C) Laboratory tests[18]

In addition to the peripheral neuropathy blood screening tests, supine and standing catecholamines, nicotinic acetylcholine receptor antibodies, alpha galactosidase (Fabry disease), subcutaneous fat pad biopsy or genetic testing (transthyretin amyloid neuropathy), antibodies for Sjogren's syndrome, plasma free metanephrines for pheochromocytoma, 24-hour urine five hydroxy indole acetic acid for carcinoid, plasma histamine for mast cell disorder, Schirmer's test and Rose Bengal test for assessment of tear production, gastrointestinal motility studies, tests for leverage in a bladder through either post-voidal residual volume or more detailed urodynamic studies are general ANS assessment studies.

The more detailed studies of sections of the sudomotor, cardio vagal and sympathetic cardiovascular tests follow.

1) In sudomotor (sympathetic cholinergic) testing the quantitative sudomotor axon reflex test (QSART) and thermoregulatory sweat test (TST) help to inform function of this arm of the ANS. It is important to rule out medication influences mediated by M3 acetylcholine receptors (atropine, oxybutynin, glycopyrrolate, amitriptyline, diphenhydramine, tolterodine. In QSART sudomotor nerves at four standard sites are tested in a quantitative manner through iontophoresis of acetone calling at the skin surface which activates an axon reflex mediated by post ganglionic sympathetic sudomotor axon and the impulse generated travels antidromically reaching a branch point in the peripheral nerve and from there travels orthodromically to evoke a sudomotor response in the adjacent eccrine glands. The evoked response is measured by the moisture detected in a capsule placed on the skin. In the TST the body is heated under controlled temperature and humidity and in this test a lesion anywhere along the thermoregulatory pathway from the brain to the spinal cord, to preganglionic nerves, to sympathetic ganglia and to post ganglionic nerves is studied with dyes that delineate colour changes mediated through sweating patterns.

2) Cardio vagal testing analyses the parasympathetic (vagus nerve) influence on heart rate by the response to deep breathing or by the Valsalva ratio. Heart rate response to deep breathing is

measured by the RR interval on ECG tracing converted to beat to beat heart rate traced along with respiration. For the Valsalva manoeuvre the recumbent patient exhales against resistance and maintains a column of mercury at 30 to 40 mmHg for 15 seconds. Power spectrum analysis of ECG signals is also possible although the "sympathovagal balance" is an unclear derivation of low-frequency power spectrum analysis.

3) Vasomotor adrenergic testing (Fig 3): dynamic changes in blood pressure during the Valsalva manoeuvre are valuable indices of baroreflex-sympathoneural function. The Valsalva manoeuvre is divided into four phases where the late phase 2 (reflex sympathetic response is first seen causing increase in peripheral vasoconstrictor tone, cardiac rate in normal subjects) and phase 4 (an overshoot in blood pressure occurs when cardiac filling returns to normal as the peripheral vasculature remains constricted in normal subjects) provide critical information. Likewise, in the tilt table test, useful in the assessment of orthostatic hypotension, orthostatic intolerance and unexplained

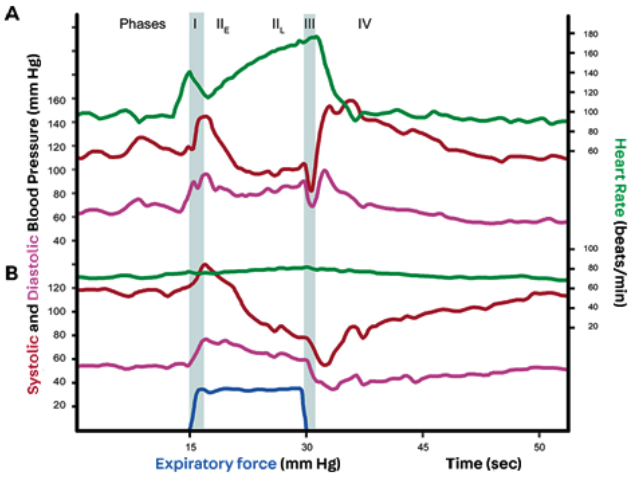

Fig 3 — Beat-to-beat blood pressure and heart rate responses to the Valsalva maneuver.

A, In healthy individuals the decrease in blood pressure during early phase II (II_E) recovers during late phase II (II_L) as the heart rate gradually increases, as an indicator of noradrenergic sympathetic outflow. During phase IV, blood pressure returns rapidly to baseline and then overshoots as cardiac output increases in the presence of peripheral vasoconstriction.

Parasympathetic vagal activation causes a decrease in heart rate. B, In a patient with multiple system atrophy (a Parkinsonian variant) with autonomic nervous system failure, the decrease in blood pressure during phase II_E persists without recovery during II_L. During phase IV, a long delay of 20 seconds for blood pressure to return to baseline is seen and no overshoot is seen. Little sympathetic cardio-acceleration or parasympathetic bradycardia is seen as there is preganglionic failure of autonomic functions

syncope, continuous beat to beat monitoring of blood pressure and heart rate is undertaken during head up tilting to 70° where in patients with baroreflex sympathoneural failure the initial BP drop does not recover and declines further and the heart rate response is decreased. In neurogenic orthostatic hypotension a response is obtained within five minutes while a longer duration of tilt is needed for delayed OH and syncope. The tilt table testing differs from active standing as there is reduced activation of leg muscles and assessment of the autonomic response to orthostatic stress is revealed.

4) Cardiac MIBG or F Dopa PET scan has become an especially important tool in the assessment of the autonomic nerve supply to the cardiac muscles. This is used to distinguish various forms of parkinsonism and primary autonomic failure and in diabetic autonomic neuropathy and that from amyloid cardiomyopathy

5) Skin biopsy for epidermal nerve fibre density measurements, used in the assessment of small fibre neuropathies, is indicative of nerve fibre loss in the epidermis and is a biomarker of autonomic neuropathy.

6) Corneal confocal microscopy has validated data in diabetic small fibre neuropathy where the arborisation of the unmyelinated fibres can be quantitatively estimated to show the loss of nerve fibres secondary to autonomic neuropathy.

7) Gastrointestinal motility studies to demonstrate functioning of the enteric plexus using various motility markers is clinically used by neurogastroenterology specialists.

8) Urodynamic studies – a whole discussion in itself and in clinical use by neurourologists

9) Microneurography – a niche test used by Neurophysiologists and pain specialists to study the subtypes of pain small fibres

10) Sympathetic skin response: not a pure pathwaytest in itself and used for overall estimation of the axon reflex and easily recorded in stimulation of the palm.

Conclusion

ANS disorders can present with brain, spinal cord peripheral nerve or dorsal root ganglia involvement and can present with orthostatic intolerance and paroxysmal vasomotor and sudomotor disorders. There is a profound effect of medications (over-the-counter and prescribed) that can influence ANS test results and patient's clinical presentation and drug interactions with polypharmacy and novel selective receptor specific new drugs that are emergent which are essential in the ANS diagnostic work up and management.

In the last few years portable or wearable smart watches and other devices are being increasingly worn by people displaying heart rate and blood pressure data is the go about their daily lives[19]. Since these are not validated many individuals who obsessively track this data as part of health monitoring may develop anxiety in patients predisposed to somatic hypervigilance. A number of companies have now entered the market with software claiming to evaluate the ANS without physician interpretation generating diagnosis and treatment recommendations as well. Till such time ICMR or FDA and suchlike health regulatory bodies approve of these gadgets careful counselling of the population needs to be undertaken to reduce anxiety for non-existent illness or treatment side effects from nonphysician advice. Simple lifestyle advice[20] goes a long way in the management of orthostatic intolerance and other autonomic nervous system disorders and a careful scrutiny of autonomic side effects of common medications we use helps avoid ANS symptoms.

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