Clinical evaluation of Dysautonomia

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Introduction: *Dysfunction of the autonomic nervous system occurs in diseases of the central/peripheral nervous system . Is important to quantify the sympathetic/parasympathetic compromise, to diagnose the dysfunction, to monitor the evolution and the response to therapies. The main functional tests are cardiovascular and sudomotor tests. There are additional examinations aimed to study the autonomic dysfunction in various organs, that are specific of the relevant medical specialties.* ***Development:*** *Symptoms are described: functional tests and study methods at cardiovascular level : sympathetic, vasomotor (noradrenergic) and cardiac vagal (cholinergic) and sweating tests: sudomotor sympathetic (cholinergic). Symptoms and examinations at a pupillary, urogenital and gastriontestinal level are described. Usefulness of autonomic functional tests in the study of various neurological pathologies is described.* ***Conclusions:*** *A joint evaluation of clinical findings and autonomic functional tests allow to determine the anatomic level and the severity degree of the autonomic dysfunction with a physiopathologic base.*

Key words: *sympathetic, parasympathetic, cardiovascular, sudomotor, pupillary, urogenital, gastriontestinal*

INTRODUCTION

The autonomic nervous system (ANS) is made up of the sympathetic nervous system (SNS) (noradrenergic, adrenergic and cholinergic), the parasympathetic nervous system (PNS) cholinergic and the enteric nervous system. The ANS rules functioning of the milieu intérieur, arterial pressure (AP), heart rate (HR), thermoregulation, breathing, gastriontestinal, urogenital and pupillary system.(1) The terms dysautonomia, and autonomic dysfunction only describe a ANS compromise; however, in the study of one patient with autonomic symptoms it is necessary to identify if the compromise mainly affects SNS, PNS, the enteric system or all three systems. ANS compromise is present in diseases: 1. Of the central nervous system, such as multiple-system atrophy, 2. of the peripheral nervous, such has diabetic polyneuropathy, 3. primary of the ANS, such as pure autonomic failure. The ANS compromise may also be functional, with no evidence of a structural lesion of the autonomic ways, such as the vasovagal syncope.(2)

Study of patients with autonomic dysfunction must be made by an expert physician who must also assess clinical/lab findings(3). Currently there are functional cardiovascular tests, sudomotor quantitative tests, noninvasive and

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reproductible tests, with a high specificity and sensitivity (≥80%).[1][4][5][6][7][8].

OBJECTIVES

In this Article we will describe symptoms and functional cardiovascular tests: sympathetic vasomotor (noradrenergic), cardiac vagal (cholinergic) and sympathetic sweating tests (cholinergic). Additionally, symptoms, signs and examinations for studying the segmentary compromise at a pupillary/urogenital/ gastriontestinal level.

DEVELOPMENT

A.- Symptoms and signs of the cardiovascular autonomic dysfunction.

Orthostatic Intolerance (IO) are symptoms and signs which show up when one stands up and are relieved in decubitus position. The most common IO symptoms are a dizziness sensation and blurred vision when quickly standing up and the syncope. IO symptoms are associated to cerebral hypoperfusion. When these symptoms are severe this may happen, because: 1. Ortostatic hypotension (OH) is defined as the drop of systolic arterial tension in 20 or more mmHg., or drop of dyastolic arterial tension in 10 or more mmHg which appears during the first 3 minutes after standing up, and lingers on till the patient goes back to a decubitus position[9]. The provisional OH may occur en presence of hypovolemia, or as a side effect from medication affecting the SNS functions, In these cases arterial pressure is recovered by correcting the triggering factor. In neurogenic OH, symptoms linger on more than 3 months and are associated to SNC or PNS diseases which compromise vasoconstrictive response of SNS to gravitational stress[10][11] Symptoms of neurogenic OH are diverse, including dizziness sensation, astenia, blurred vision, syncope, weakness in lower limbs, pain in the suboccipital and para cervical regions, disnea, transitory cognitive dysfunction, such as memory and concentration deficit, tremors, intolerance to exercises[12][13][14]. These symptoms may get worse in a warm environment or after abundant meals (postprandial hypotension) [15]. In patients with dementia, OH symptoms are harder to be recognized[16] 2. In the postural orthostatic tachycardia syndrome (POTS) there is presence of IO symptoms with no OH symptoms and with a steady increase of the FC with more than 30 beats per minute, or equal or higher than 120 beats per minute, when standing up and remain steady while the patient is standing.[17] 3. In a syncope a transitory IO occurs with sudden loss of consciousness, and a short duration (less than 20 seconds), with instant recovery, due to a transitory encephalic hypoperfusion. The syncope may be cardiogenic due to a sudden drop of the cardiac impairments (arrhythmias, myocardial infarction, aortic stenosis and others). In vasovagal syncope (VV) or neurally mediated there is transitory autonomic instability, with bradycardia and/or vasodilatation along with AP drop. In SVV some prodromal symptom arise, such as dizziness, blurred vision, fatigue and symptoms of autonomic activation with presence of sweating, abdominal discomfort and nauseas. In the vasovagal syncope it is possible to identify triggering factors, such as standing up, warm environment and emotional stress. Also the syncope may be a reflection, caused by un coughing fit, caused by miccional effort, increased sensitivity of the carotid sinus[18][19].

Examinations for the study of Cardiovascular Autonomic Dysfunction

A.- Functional Tests of the Sympathetic Nervous System.

1. Orthostatic stress: the active postural change measures AP and FC with the patient in a decubitus position and then standing, during 3 to 10 minutes. The passive postural change can also be used with the tilt table. This last method allows a prolonged record, useful to search for a retarded OH which shows up after 3 minutes while standing and it is a mild form of neurogenic OH[20]. It is important to consider that patients without a history of VV syncope may have high susceptibility to arterial hypotension during the tilt table maneuver[19][21].

2. Valsalva Maneuver: the patient forces out his/ her breath against a resistance of 40 mmHg, for 15 seconds. There is an increase of intrathoracic pressure with drop of the venous return and transitory drop of the systolic ejection with AP drop (early phase II) after the activation of the

baroreceptors it causes a sympathetic activation with an increase of the AP (late phase II) and when finishing the maneuver there is a higher increase of the AP, due to recovery of the systolic ejection and the sympathetic activation (phase IV) and a posterior bradycardia [21,22].
3. Change of the AP with the isometric exercise. The patient must hold a dynamometer in his/her hand, with a strength of 30% of the maximum strength, during 3 minutes, the previous AP is measured and every one minute during the maneuver. The difference between dyastolic arterial tension is measured at the end of the exercise and previous dyastolic arterial tension. The normal value is an increase of ≥ 10 mmHg [4]. The measurement of the Valsalva Maneuver and the isometric exercise
A digital plethysmograph (Finapres) allows to continuously monitor the AP.

B Functional Tests of the Parasympathetic Nervous System (cardiovagal)

1. Maximum Breathing Test. It measures heart rate response to deep breathing. The subject breathes 6 times per minute, during breathing tachycardia occurs. While breathing out bradycardia occurs, due to the sinus arrhythmia whose cardiorrespiratory integration depends on a afferent pathway and cardiovagal efferent pathway[(1)(5)]. The maximum FC minus the minimum FC en each breathing cycle is measured and FC variations are averaged. The normal value is ≥ 10 beats per minute[(6)(7)]. 2. Index of Valsalva, the Valsalva Maneuver. This test also assesses the response cardiovagal, during the maneuver the function of the vagus nerve with tachycardia and activation after the maneuver with bradycardia is inhibited. During the maneuver, the maximum FC is divided by the FC, after the maneuver. The normal index

Table 1. Clinical study of the Cardiovascular Autonomic Function

Compromise	Efferent pathway	Clinic	Functional studies
Noradrenergic sympathetic vasomotor	Ventrolateral bulb spinal chord CIL Sympathetic ganglia	Ortostatic hypotension Orthostatic intolerance Syncope	Tilt table: AP postural change measurement plasmatic catecholamines Valsalva Maneuver: AP change Isometric exercise (“hand grip”)
Cardiovagal Parasympathetic	Ambiguous nucleus bulb Cardiac ganglia	Fixed tachycardia	Maximum breathing test (FC variation) Valsalva Maneuver: FC change Index 30:15
Baroreflexes dysfunction	Sympathetic and Cardiovagal	transitory tachycardia AP Instability	Baroreflexes sensitivity test

Arterial Pressure=AP, CIL = intermediolateral columns , heart rate =HR

of Valsalva is ≥ 1.20[22]. 3. Index 30:15, the patient must be in a decubitus position and must stand up with no help. Usually an immediate increase of the FC that is maximum around beat #15, after remaining standing, followed by an FC decrease that is maximum around beat # 30. The longest R-R intervals are divided by the shortest R-R. The normal index is ≥ 1.01. In healthy patients maximum breathing test values, from the Valsalva Indexes and 30:15 progressively decreases with age[23][24][25].

C.- Other Study Methods:

1. Measurement of plasmatic catecholamines in a decubitus position and standing: The value of the plasmatic norepinephrine under rest condition states the activity of the central and peripheral pathways of the SNS noradrenergic. This value is doubled within the first 5 minutes when remaining standing. En patients with neurogenic OH the norepinephrine does not increase with the postural change[26].

2. Outpatient monitoring of Arterial Pressure: AP control during 24 hours is useful to determine AP fluctuations in patients with neurogenic OH as AP drops after meals or with physical activity. Patients also have arterial hypertension in a decubitus position and an inversion of the AP circadian rhythm, with loss of nocturnal physiological drop[27][28]

3. Heart Images: It is possible to visualize the sympathetic innervation of the heart by means of a gammaradiography, using markers, such as 123imetaiodobenzylguanidine (123I-MIBG), in cases of sympathetic denervation it decreases myocardial pickup .[28]

5. Functional Study of the Baroreflexes: By means of a PA/FC continuous record, using a digital Photoplethysmograph during the Valsalva Maneuver, changes of the FC are measured in relation with the AP variations, and a value of the sensitivity of the Baroreflexes is obtained[5][29].

The spectral analysis of the heart rate is used exclusively in clinical investigation[5].

B.- Symptoms and Signs of Autonomic Dysfunction during sweating.

Anhidrosis is the absence of sweating in ambient/physiological conditions which normally activate sweating and is manifested by heat intolerance. Anhidrosis occurs due to a lesion in the sympathetic efferent pathway at a central level (hypothalamus, brainstem, spinal cord) or a peripheral level (cholinergic sympathetic innervation of the sweat glands)[1]. In cases of peripheral polyneuropathies affecting the thin fibers an anhidrosis of distribution distal occurs. Anhidrosis may be local/generalized, depending on the distribution of the sympathetic compromise . Absence of sweating may also be a side effect of dermatologic/metabolic pathologies and a side effect of medication (with anticholinergic action). Hyperhidrosis is excessive sweating, exceeding the amount used for controlling body temperature. Hyperhidrosis may be generalized when affecting the whole body or segmentary. Generalized hyperhidrosis may occur in pathologies, such as infections, tumors, endocrine/metabolic diseases as a side effect of medication and neurological causes, such as Parkinson and cerebrovascular accidents. Segmental hyperhidrosis may be a primary cause, and it occurs at the hands palms, feet soles, armpits and head. Secondary causes may correspond to a compensatory segmentary hyperhidrosis with presence of anhidrosis in other parts of the body[30].

EXAMINATIONS FOR THE STUDY OF SUDOMOTOR FUNCTION

Functional tests.

1. Thermoregulatory sweat test (TST): It studies the sweating sympathetic pathways at central/peripheral level. The patient remains in a chamber and body temperature is increased in 1° C to start sweating, which is detected by applying colorant (Quinizarin) This technique allows to quantify body sweat corporal ventral and limit anhidrosis areas.[31] 2. Quantitative Sudomotor Axon Reflex Test (QSART), uses iontophoresis of acetylcholine at 10% to activate the sweat gland. Local sweat is measured by the change of humidity in a capsule. A direct change is measured in the activation place and an indirect change resulting from the axon reflex activation. This Test allows to identify peripheral lesions of the sudomotor pathway[8] [31].

Other study methods:

1. Cutaneous Sympathetic Response: it depends on the activity of the sweat glands. it measures electrical activity changes on the skin evoked by stimuli (electrical, hearing, deep breathing). The patient must be at rest, in a supine position. This response is measured on the hand palm and the sole of the foot. An electromyograph is used. The active electrode is set (negative) on the palm or the sole. Positive electrode is set on the back of the hand or the foot. This cutaneous response results from the activation of the sympathetic efferent pathway, from the hypothalamus to the peripheral cholinergic innervation, therefore, an abnormal response (low amplitude) does not indicate if the level of compromise is central or peripheral[1] [32]. Another indirect tests measures changes

Table 2. Study of the Sudomotor Sympathetic Function

Compromise	Efferent pathway	Clinic	Functional studies
Central Preganglionic	Hypothalamus Spinal chord CIL	Hemianhidrosis Hemihyperhidrosis Compensatory hyperhidrosis	Thermoregulatory sweat test (TST)* Sympathetic cutaneous response*
Peripheral Postganglionic	Sympathetic ganglia Sympathetic axons to the sweat gland	Distal anhidrosis Segmentary anhidrosis Compensatory hyperhidrosis	Quantitative Sudomotor Axon Reflex Test (QSART) Silicone impression of quantitative sweat (QDIRT) Electrochemical conductance**

CIL = intermediolateral columns ,
QSART = Quantitative sudomotor axonal reflex test,
QDIRT = Quantitative Direct and Indirect sudomotor test
* Test aimed to detect sudomotor compromise pre and post ganglionic,
** Indirect Test. Level of sudomotor compromise detected is not known

on skin conductance (chlorine ion of the sweat gland) induced by a reveres iontophoresis[8]. Other tests have been described to evaluate the postganglionic sudomotor function as the silicone impression of sweat drops (iontophoresis of acetylcholine)[1], direct/indirect quantitative sweat test (QDIRT), spatially measures the postganglionic function of the sweat gland (iontophoresis of acetylcholine[8]. (Table 2) Cholinergic innervation study of the sweat gland with skin biopsy is also useful, using immunohistochemistry techniques[33].

C.- Segmentary Study of Autonomic Dysfunction

I.- Pupillary Autonomic Compromise. Normal pupillary size results from the balance between the opposed influence of the parasympathetic tone which causes muscle contraction of the iris (miosis) and of the sympathetic tome which dilates the pupilla (mydriasis). A lesion in the parasympathetic pathway causes pupillary mydriasis (prevalence of the sympathetic tone) and in lesions in the sympathetic pathway miosis occurs (prevalence of the parasympathetic tone). Sympathetic pupillary compromise represents Horner Syndrome, which includes miosis, palpebral ptosis (compromise of Müller muscle) and facial anhidrosis all over the face (preganglionic lesion) and an area in the frontal region (postganglionic lesion)[34].

Examinations:

1. Pharmacological tests: Parasympathetic, the use of pilocarpine eye drops diluted at 0.0625%

which in a normal pupilla does not cause changes due to dilution, in the pupilla with denervation of the ciliary ganglion (Adie pupil) meiosis occurs, due to a hypersensibility caused by denervation of the iris muscle. Sympathetic: cocaine eye drops at 4% dilates a healthy pupilla, but it does not dilate a pupilla with sympathetic denervation. Hydroxyamphetamine eye drops at 1% dilates a normal pupilla and causes high dilation in preganglionic lesions, en postganglionic lesions there is no pupillary change. The eye drops of phenylephrine at 1% does not dilate a healthy pupilla as it is diluted[35].

2. Pupillometry: In parasympathetic denervation a slow redilation may happen.

II.- Urogenital autonomic compromise

Neurogenic bladder: the presence of vesical dysfunction with hyperactivity or hyperactivity of the detrusor muscle, with no obstruction of the urinary tract, may cause a hard urine emptying/filling process.

1. Hyperactive bladder: this compromise is localized at a central level: brain (frontal lobe and basal ganglions), storage capacity of urine is reduced and has symptoms of increasing frequency and miccional urgency. Lesions located between the brainstem (pontine nucleus of the miction) and the lumbosacral spinal cord, cause hyperactivity of the detrusor muscle and dyssynergia of the detrusor-external sphincter urethrae, with presence of miccional urgency along with incontinency and weak mictional flow.

2. Vesical ultrasound Bladder: it happens in lesions of the sacral center of the miction and in peripheral neuropathies caused by parasympathetic denervation of the detrusor muscle . Emptying bladder is difficult, which may progress till urinary retention. These patients may have overflow urinary incontinence[36].

Examinations

Vesical ultrasound, measuring post mictional residue. Residues
higher than 100 ml are considered as hypoactive bladder[37]. Urodynamic studies, such as cystometry evaluates the function of the detrusor muscle during vesical filling. It is useful to quantify a hyperactive bladder, to measure the flow, which depends on contraction of the detrusor muscle and resistance of the external sphincter urethrae (measured with electromyography). Measurement allows to diagnose external detrusor-sphincter urethrae dyssynergia (38) (39)(40). Erectile dysfunction is multifactorial, in SNC and PNS diseases it may be associated to parasympathetic denervation of the muscles relaxing the corpus cavernosum (mediated by nitrous oxide). The study includes valuation of the nocturnal penile tumescence, sonography and neurphysiological methods. In neurogen erectile dysfunction diagnosis it is important to discard psychological causes and medication side effects[39]. A sympathetic compromise may also cause retrograde ejaculation[39]. In women lack of vaginal lubrication may be a sign of parasympathetic dysfunction .

III Gastrontestinal Autonomic Compromise

Slow esophageal motility causes dysphagia and regurgitation. Gastroparesis is caused when gastric emptying is slowing down, in absence of mechanical obstruction. Symptoms include gastric discomfort, early satiation, nauseas, vomitting and sensation of gastric distension. At intestinal level symptoms are chronic constipation and intermittent diarrhea. Neurogenic incontinency is mainly due to motor lesions (pudendal nerves) and sensitive lesions (spinal cord) and it is not a symptom of exclusive autonomic compromise.[41][42]. Examinations: for study of the patients with gastrointestinal motility disorder, first endoscopic examinations and imagery must be done in order to discard obstructive lesions. Compromise of the vagus nerve at the medulla oblongata or in the efferent pathways, affect motility of the esophageal/gastric wall. Videofluoroscopy studies esophageal motility . In the stomach isotopic studies of gastric emptying and the record of gastric muscles electrical activity are used (electrogastrography). peristaltic movement of the intestine mainly depend on enteric nervous system and on paravertebral sympathetic innervation inhibiting motility[43]. In constipation studies it is important to identify intestinal motility slowing down associated to autonomic dysfunction. Parasympathetic

innervation (sacral spinal cord) regulates motility of distal colon and rectum. Evaluation of defecating disorders includes imagery and manometry[39]

Questionnaires of Autonomic Symptoms.
There are some instruments allowing to quantify symptoms of the various ANS domains: the questionnaire SCOPA-AUT was originally designed to evaluate the autonomic symptoms in Parkinson. It has 23 questions about 6 areas: gastrointestinal, orthostatic intolerance, sweating, urinary, pupillary and sexual[44], this questionnaire has been validated in Spanish[45]. Questionnaire COMPASS ("Composite Autonomic Symptoms Scale"), has 72 questions about orthostatic intolerance, vasomotor changes, sweating, urinary symptoms, gastroparesis, constipation, diarrhea, syncope, sleep disorders and erectile dysfunction[46]. This questionnaire has also been validated in Spanish[47]
Main Clinical Indications for the study of ANS function:

A.- General directions:
1. To objectively state the presence of ANS compromise
2. In order to determine anatomical/physiological distribution of the pre/postganglionic, isolated or generalized compromise of the ANS.
3. To re-asses the degree of severity of the ANS compromise.
4. Obtain objective information about the progression of the disease or about response to therapies.
B.- Specific Indications:
1. In order to determine if the OH is neurogenic and to evaluate the degree of sympathetic vasomotor compromise.
2. Study of the syncope of uncertain causes and to tell VV syncope from the psychogenic syndrome and to state the vasodepressor/ cardioinhibitory component of the VV syncope.
3. To study postural tachycardia (POTS) and the retarded OH.
4. In Parkinson, Multiple-system atrophy (parkinsonian/cerebellar subtype), Dementia with Lewy bodies and pure autonomic failure the study of the ANS helps to determine severity and to differentiate between various etiologies.
5. Peripheral polyneuropathies allow to evaluate severity and distribution of the compromise of the autonomic fibers in hereditary/ acquired neuropathies (diabetic, amyloidosis, paraneoplastic, Guillain Barre, infectious). (Table 3).
6. In patients with isolated autonomic dysfunction symptoms (pupillary, sudomotor, genitourinary) to determine the degree of compromise and to study if additionally there is a subclinic compromise in other ANS levels

Considerations about Autonomic Tests.
1. The tests to study ANS are an extension of the clinical record and physical examination; therefore, the physician who interprets the results must have a training on neurology and on ANS pathologies[48]The clinical study and the tests must be performed in the same session, so that the physician may supervise and interpret the information in real time[49]
2. Before performing the study it is necessary to identify the potential factors which may modify the answers of the tests, such as: hydration, emotional stress, consumption of caffeine, alcohol, nicotine, medication anticholinergics, sempatomimetik and the existence of primary pathologies of the organ (heart, skin, eye). The patient must stop using the medication which alters autonomic function 8 hours before; coffee, alcohol and nicotine 12 hours before.

CONCLUSIONS

The tests to study ANS allow to objetivate compromise presence of SNS, PNS and SNE, helping to locate the anatomical/functional distribution of the autonomic dysfunction, assess the evolution and response to specific therapies. The tests must be performed along with the sympathetic compromise and parasympathetic, in such a way as to define the extension and severity of the compromise. These must include at least 2 domains (cardiovascular and sudomotor), and to be complemented with segmental tests, according to the clinical picture of the patient. Is important to highlight that these tests are an extension of the clinic exploration.

Table 3. Usefulness of autonomic functional tests in various clinical diagnosis.

Clinical Diagnosis	Tests				Clinical Usefulness of the functional tests
	Postural change AP, FC	Valsalva AP, FC	Cardio Vagals	Sweat	
Hypotension Ortostatic	X	X			To determine if it is a neurogenic cause To evaluate severity and temporary profile
Syncope	X				To evaluate syncope with no precise cause To recognize psychogenic syndrome During the VV syncope to evaluate AP and FC
Intolerance Ortostatic	X				To evaluate postural tachycardia To evaluate the retarded ortostatic hypotension
Disorder Neurodegenerative	X	X	X	X	To evaluate dysfunction in Parkinson, A. multisystemic, dementia, Lewy bodies To distinguish between E. Parkinson and A. multisystemic To distinguish between A. multisystemic and other ataxias To study the pure autonomic failure
Neuropathy Peripheral	X	X	X	X	To evaluate the distribution of the compromise, the severity of the dysfunction. To evaluate the small fiber neuropathy

Arterial Pressure=AP, Heart Rate =HR, VV = Vasovagal, D = Disease, A = atrophy

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