REVIEW ARTICLE

Dysautonomia in the older patient: clinical presentation and assessment.

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Abstract

The Autonomic Nervous System is represented by neurons in ganglia outside the brain and spinal cord that seemed to have functions independent of the Central Nervous System. Autonomic failure may be due to primary autonomic disorders such as Multiple System Atrophy or Pure Autonomic Failure or be secondary to diseases, such as diabetes mellitus or malignancies.

The temporal profile of the disease and its manifestations may be either acute, subacute for post-infective or paraneoplastic syndromes, or chronic for diabetes, alcoholism, and amyloidosis. Autonomic dysfunction may result in impairment of cardiovascular, thermoregulatory, gastrointestinal, urogenital, sudomotor, and pupillomotor functions in different combinations and degrees of severity. Orthostatic hypotension is a frequent cause of syncope, especially in the older patient; is the main feature of cardiovascular autonomic failure in clinically established Multiple System Atrophy, but may also be drug-related, or be the first manifestation of malignancy or anemia.

The present paper will discuss the different causes of dysautonomia in the older patient, focusing on neurodegenerative forms and paraneoplastic neuropathies, from clinical presentation to differential diagnosis.

Keywords: cancer, older patient, dysautonomia, orthostatic hypotension, syncope, autonomic neuropathy.

An 81 years old man presented with orthostatic intolerance started one year before and worsened during the hot season, leading to orthostatic and post-micturition syncopal episodes.

During the two years before, the patient also reported constipation, xerostomia and xerophtalmia, REM sleep behavior disorder, coexistent loss of strength and movement impairment on his right hand, without rigidity, bradykinesia or tremor.

Introduction on Autonomic Nervous System

Langley, introduced the term "Autonomic Nervous System" (ANS) about a century ago, and used it to refer to neurons in ganglia outside the brain and spinal cord that

seemed to have functions independent, or autonomous, of the Central Nervous System (CSN) [1, 2].

The ANS has multiple components: the sympathetic nervous system (SNS), parasympathetic nervous system (PNS), and enteric nervous system (ENS). The SNS is composed of two subsystems based on their main chemical messenger norepinephrine (NE), epinephrine (E) and acetylcholine (Ach). The sympathetic noradrenergic system (SNaS) is the SNS component responsible for reflexive constriction of blood vessels and stimulation of the heart. The sympathetic cholinergic (SChS) system mediates sweating. The PNS is responsible for a constellation of phenomena including respiratory sinus arrhythmia, gastrointestinal and urinary bladder tone, salivation, lacrimation, and pupillary constriction in response to light. Cannon, in the early 20th century, added a hormonal component, the sympathetic adreno-medullary system (SAS), which uses E as the chemical effector [3, 4]. E is one of the three main hormones regulating serum glucose, the others being insulin and glucagon [5].

Proper functioning of the ANS requires that both afferent and efferent limbs are intact. Afferent neurons detect changes in blood pressure (BP), temperature, and the myriad of other vital processes controlled by the ANS, and communicate these changes centrally, whereas the efferent neurons engage effector systems to perturb or restore homeostasis.

Pathogenesis of autonomic failure

Autonomic failure may be due to primary autonomic disorders such as Multiple System Atrophy (MSA, Shy-Drager syndrome) or Pure Autonomic Failure (PAF) or be secondary to diseases, such as diabetes mellitus, amyloidosis, or malignancies.

The different causes of autonomic failure are listed in Table 1, [6].

Table 1: Causes of autonomic failure, adapted from Bennaroch E.E, [6]

Isolated autonomic failure
1. Acute or subacute
(a) Autoimmune autonomic ganglionopathy
(b) Paraneoplastic autonomic neuropathy
2. Progressive
(a) Pure Autonomic Failure
Progressive autonomic failure associated with parkinsonism, ataxia or dementia
1. Multiple System Atrophy
2. Lewy body disorders
(a) Parkinson disease
(b) Dementia with Lewy bodies
3. Others
(a) Familial leukoencephalopathies
(b) Prion disorders
Autonomic failure associated with peripheral neuropathy
1. Chronic sensorimotor neuropathies
(a) Diabetes

(b) Amyloidosis
(c) Other metabolic disorders (vitamin B_{12} deficiency, uraemia)
(d) Toxic neuropathies
2. Sensory ganglionopathies
(a) Sjögren syndrome
(b) Paraneoplastic
3. Distal painful neuropathies
(a) Diabetes
(b) Amyloidosis
(c) Idiopathic (sodium channelopathies)
(d) Infectious (HIV)
(e) Hereditary
(i) Hereditary sensory and autonomic neuropathy
(ii) Fabry disease
(iii) Sodium channelopathies
4. Acute or subacute motor polyradiculopathy or neuropathy
(a) Guillain–Barré syndrome
(b) Porphyria
5. Acute autonomic and sensory neuropathy
6 Ross syndrome (segmental anhidrosis, Adie pupils and areflexia).

Neurodegenerative autonomic failure syndromes

Multiple system atrophy

Multiple System Atrophy is an adult-onset, neurodegenerative disorder of presumed sporadic origin, morphologically characterized by proteinaceous oligodendroglial cytoplasmic inclusions, called Papp–Lantos bodies, with neuronal multisystem degeneration. The main constituent of glial cytoplasmic inclusions is misfolded alpha-synuclein, a protein normally located in neuronal axons and synapses [7].

Although MSA is considered a sporadic disease, a mutation of the coenzyme Q2 gene in Japanese families with MSA has been identified, and *COQ2* variants were also associated with an increased risk of sporadic MSA [8].

MSA clinical features are represented by autonomic failure and motor impairment with variable combinations of poorly levodopa (L-dopa)–responsive parkinsonism, cerebellar ataxia, and corticospinal tract dysfunction. It is classified into two subtypes, depending on the predominant motor presentation: (1) a parkinsonian variant reflecting underlying striato-nigral degeneration (SND) MSA-P and (2) a cerebellar variant associated with olivo-ponto-cerebellar atrophy (OPCA)—MSA-C. Although there may be different genetic susceptibility factors between MSA-P and MSA-C, there is no evidence of different pathogenesis between subtypes [9].

Orthostatic hypotension (OH), which appears early in the disease, depends on the involvement of preganglionic sympathetic neurons and sympatho-excitatory neurons of the rostral ventrolateral medulla [6]. OH is the main feature of cardiovascular autonomic failure in clinically established MSA, and is defined as a blood pressure decrease of 30 mm Hg systolic or 15 mm Hg diastol-

ic within 3 minutes of passive head-up tilt or standing from the recumbent position [10]. Postprandial hypotension, supine and nocturnal hypertension accompany OH in half of patients [11].

Urogenital and sexual dysfunction may be the first clinical features. The patient may suffer for urinary urgency, followed by incontinence and incomplete bladder emptying, due to a combination of detrusor hyperreflexia and urethral sphincter weakness followed by detrusor contraction failure [12].

A manifestation of brainstem neurodegeneration is sleep-related breathing impairment. MSA patients may indeed experience sleep apnea and laryngeal stridor, due to impaired automatic ventilation and laryngeal dystonia with inspiratory adduction of the vocal cords [13].

Dementia or visual hallucinations are rare and, when associated to parkinsonism and autonomic failure, should prompt consideration of dementia with Lewy bodies (DLB) [11]. Patients with MSA may present with inappropriate laughing or crying in the absence of the appropriate emotional context, depression, anxiety, panic attacks, and suicidal ideation [14]. Finally, as many as 50% of patients report disabling pain [7].

Pure autonomic failure

Pure Autonomic Failure is a rare, sporadic, adult-onset disorder characterized by symptomatic OH and variable gastrointestinal, bladder and sexual dysfunction, without somatic motor deficits [6].

Degeneration of peripheral autonomic neurons along with alpha-synuclein inclusions, Lewy body–like, in sympathetic ganglia and widespread alpha-synuclein deposits in autonomic neurons, are characteristic and enable to establish PAF as a restricted, non-motor synucleinopathy [15]. The involvement of central structures is suggested by the presence of REM sleep disorder and anosmia [16], and by the spinal fluid catechol profile suggesting involvement of central noradrenergic and dopaminergic neurons [17].

Symptoms are less progressive and disabling than other neurodegenerative disorders. The diagnosis of PAF requires at least a 5 year history of isolated autonomic dysfunction without other neurological manifestations, as after few years, many patients with presumed PAF may develop cerebellar, extrapyramidal or cognitive deficits indicating MSA, Parkinson disease (PD) or DLB [18].

Parkinson disease

Parkinson Disease is mainly characterized by motor symptoms such as bradykinesia, rigidity, tremor and postural instability. In addition, PD patients may also suffer from non-motor symptoms, as behavioral, sleep or perception dysfunctions as well as dysautonomia [19]. This latter occurs more frequently on advances stages of the disease, and influences treatment and quality of life [20].

Dysautonomia is related to the almost ubiquitous loss of neurons and the appearance of Lewy bodies within completely different parts of the nervous system. Braak et al.[21] explained lesions in the dorsal vagal nucleus and in other autonomic cerebral stem centers within PD patients, already before any clinical period, as well as before the appearance of characteristic histopathological changes in the subtantia nigra.

Autonomic Peripheral Neuropathies

Peripheral, postganglionic, disorders affect the neurons of the autonomic ganglia and the small lightly myelinated and unmyelinated autonomic nerve fibers extending to the target organs.

The temporal profile of the disease and its manifestations may be either acute, sub-

acute for post-infective or paraneoplastic syndromes, or chronic for diabetes, alcoholism, and amyloidosis [22].

Symptoms of autonomic dysfunction, including impairment of cardiovascular, gastrointestinal, urogenital, thermoregulatory, sudomotor, and pupillomotor autonomic function, are either the only features or the predominant clinical features often masking the symptoms of somatic small fiber involvement. The increased availability of autonomic testing, combined with other neurophysiologic studies and skin biopsies, has allowed for increased detection of autonomic dysfunction and small fiber neuropathies [23].

Autoimmune Autonomic Ganglionopathy

Autoimmune Autonomic Ganglionopathy (AAG) includes a group of acquired disorders characterized by diffuse autonomic dysfunction with an immune-mediated pathophysiology and positivity of ganglionic nicotinic α3-acetylcholine receptors (α3-AChR) autoantibodies. Frequently patients experience a viral upper respiratory tract or gastrointestinal infection, before manifesting the autonomic dysfunction. AAG may also be associated with vaccination, surgery, or interferon therapy [24]. Classically, AAG is a subacute disorder with monophasic onset, partial spontaneous improvement, and high antibody levels (>0.5 nmol/L, normal <0.05). However, some cases of slowly progressive autonomic dysfunction may actually represent limited forms of AAG [25]. Patients with features of AAG, however, frequently have an associated malignancy, most of which are considered paraneoplastic syndromes [26].

Paraneoplastic Autonomic Neuropathies

Paraneoplastic neurological syndromes (PNS) are disorders of the nervous system occurring in association with a cancer, not related to any metabolic, infectious, degenerative, metastatic or iatrogenic cause. PNS are thought to be secondary to an autoimmune reaction against neuronal antigens ectopically expressed by the underlying tumor [27].

The most typical paraneoplastic neuropathy is the subacute sensory type, usually associated with small-cell lung cancer and anti-Hu antibody [28]. Paraneoplastic neuropathy can show a wide variety of symptoms ranging from sensory ataxia to painful sensory impairments. When small myelinated and unmyelinated fibers loss is predominant, pain symptoms are mostly present, particularly mechanical hyperalgesia associated with no or only a mild degree of sensory ataxic symptoms. The ataxic form patients show a loss of predominantly large-myelinated fibers. A sensory ganglionopathy, that affects mainly small ganglion neurons, is most likely responsible for the painful version of paraneoplastic neuropathy [29, 30].

Paraneoplastic syndromes may also manifest as autonomic dysfunction, predicting a worse prognosis, and are associated with paraneoplastic antibodies such as anti-Hu and anti CV2/CRMP-5 [31, 32]. In approximately 21% of patients, antiganglionic Ach-receptor antibodies are related to autonomic paraneoplastic neuropathies [33].

Symptoms of autonomic neuropathy may vary from OH, sicca syndrome, pupil involvement, urinary retention, sexual dysfunction, and gastrointestinal dysmotility [34]. Paraneoplastic chronic gastrointestinal pseudo-obstruction is a rare condition, which may be associated with small cell lung carcinoma, thymoma, gynaecological, and breast cancer, and should be considered as a differential diagnosis in otherwise unexplained gastrointestinal motor dysfunction. The presence of autoantibodies against antigens shared by tumour cells and by enteric neurones (onconeural antigens, like anti-Hu, anti-VGCC, and anti-ganglionic

acetylcholine receptors), has been hypothesized. Gastrointestinal symptoms usually precede tumor discovery, but not all cases have an underlying tumor [35].

All patients with malignancies should be screened for paraneoplastic neuropathy. The diagnostic process may be helped by whole-body positron emission tomography (PET) or computed tomography (CT) scan, to detect malignancies that cannot be detected by conventional tests.

The main therapeutic approach is to treat the underlying tumor. Immunomodulatory therapy can be beneficial in some cases [36].

Clinical presentation

Autonomic disorders manifest with autonomic failure or hyperactivity, which may be generalized or focal, and can result from lesions at any level of the Central or Peripheral Nervous System. Sympathetic failure manifests primarily with OH and anhidrosis, cranial parasympathetic failure with intolerance to light, xerophthalmia and xerostomia, sacral parasympathetic failure with urinary retention and erectile dysfunction, and enteric nervous system failure with gastroparesis and constipation.

The temporal profile of onset and progression of autonomic dysfunction has important diagnostic implications. When isolated autonomic failure has an acute or subacute onset, it could be related to an immune cause such as AAG, paraneoplastic autonomic neuropathy, or drug-induced. PAF refers to the slow development of generalized autonomic failure in the absence of motor or sensory symptoms. Chronic and progressive generalized autonomic failure, such as ataxia or parkinsonism, suggest a degenerative cause, typically a synucleinopathy such as MSA, PD or DLB.

Orthostatic Hypotension

Orthostatic Hypotension is defined as a fall in systolic blood pressure (SBP) from a baseline value ≥ 20 mmHg or diastolic BP (DBP) ≥ 10 mmHg or a sustained decrease in SBP to an absolute value <90 mmHg within 3 minutes of standing [37]. Since the magnitude of BP drop also depends on baseline values, it was suggested that a drop of 30 mmHg may be a more appropriate criterion for OH in patients with supine hypertension [38]. OH may manifest as recurrent syncope, light-headedness, weakness, nausea, tremulousness, headache, or "coat-hanger pain" (pain in the neck and shoulder region) on standing, but it may also be asymptomatic [11].

OH rate increases with age, reaching 24% in the 8th decade and 31% in the 9th decade [39] and has a prevalence of 24% in patients older than 65 years old consecutively referred to the Emergency Department for a transient loss of consciousness [40].

The circulatory autonomic causes of orthostatic intolerance include initial OH (IOH), classical OH (COH), and delayed OH (DOH). *Initial* OH is represented by a BP decrease of > 40 mmHg for SBP and/or >20 mmHg for DBP within 15 seconds of standing, with quick and spontaneous recovery, which is detectable by beat-to-beat BP monitoring [37]. IOH may have implications in older adults, particularly when on cardiovascular medications [41]; approximately 15% of long-term care residents fall after rising to standing, and initial OH could potentially exacerbate this falling risk [42].

C*lassical* OH is detected on active standing or passive standing on head-up tilt of at least 60°, within 3 minutes of standing.

Delayed OH is defined as OH occurring beyond three minutes of active standing or passive standing on head-up tilt and is characterized by a slow and progressive decrease of SBP. Hypotension can manifest

clinically up to 30 minutes after the achievement of the upright position, and passive head-up tilt is needed for the diagnosis [37]. DOH is common in the older patient, due to impairment of compensatory reflexes and stiffer hearts more sensitive to a decrease in preload. It may also represent a mild form of COH, especially if associated with parkinsonism or diabetes [43].

Pharmacotherapy and dehydration are the primary causes of OH in the older patient. A drug regimen based on alpha-receptor blockers, nitrates or benzodiazepines, was found to be a predictor of OH in this age group [39]. Neurogenic OH is the manifestation of impaired sympathetically mediated vasoconstriction of skeletal muscle and mesenteric vessels in response to baroreceptor unloading due to orthostatic stress, and may depend on primary autonomic failure (e.g. idiopathic PD and MSA) or secondary autonomic failure (e.g. diabetic and alcoholic autonomic neuropathy). Occasionally OH may be the first manifestation of malignancy or anemia, which should be excluded particularly in the older population [44].

Sweating impairment

The Sympathetic Nervous System mediates sweating through cholinergic activation of muscarinic M3 receptors in the eccrine sweat glands, contributing to an important thermoregulatory activity. Anhidrosis in autonomic failure may reflect impairment at different levels, central or peripheral, and depending on its distribution and severity, might be asymptomatic or manifest with hyperhidrosis in unaffected areas or heat intolerance [45].

Gastroenteric dysmotility

The Enteric Nervous System, modulated by vagal and paravertebral sympathetic inputs, controls the gastrointestinal motility. Dysphagia and regurgitation are manifestation of delayed esophageal transit. Delayed gastric emptying produces early satiety, anorexia, nausea, postprandial vomiting, and pain. Lower gastrointestinal dysmotility manifests with constipation and/or diarrhea [46].

Bladder and sexual dysfunction

Impaired micturition can result from lesions affecting afferents to the bladder, sacral parasympathetic neurons or their axons, or cholinergic muscarinic neurotransmission. Neurogenic bladder can manifest with detrusor hyperactivity, leading to urinary urgency with or without incontinence, urinary frequency, and nocturia. The detrusor underactivity is responsible for incomplete bladder emptying, urinary retention and overflow incontinence. Neurogenic bladder may be associated with erectile and ejaculatory dysfunction in men and poor vaginal lubrication in women [47].

Clinical evaluation

The clinical history should include the collection of systemic diseases, physical frailty and locomotor disabilities. Details of cognitive status, impact of symptoms on confidence and ability to carry out basal/instrumental activities of daily living independently, should also be recorded. The clinical history regarding syncopal/presyncopal episodes should be pursued by a witness' account for the relevant presence of retrograde amnesia in the older patient. Particular attention should be paid to the time of the day, season, relationship with meals, nocturnal micturition, supine or upright position, drugs, duration of treatment and time-relationship between drug consumption and appearance of adverse effects [37].

Precise details of the drug regimen should be collected as numerous drugs, e.g., alpha-receptor blockers, nitrates or benzodiazepines, are predictors of OH. Therefore, attention should be paid to reappraisal of the

drug regimen in the presence of OH in order to reduce syncope recurrence [39].

A comprehensive cardiovascular and neurological assessment, searching for PD or other neurodegenerative conditions related to autonomic dysfunction, coupled with a careful observation of gait and standing balance for the evaluation of the locomotor system and the consequent risk of falling, are mandatory steps of the physical examination.

The clinical evaluation should also include: assessment of pupil size, symmetry and reactivity with both bright and dim light; active standing test (measurement of BP in the supine position and then immediately after changing from the supine to the upright position and after 1 and 3 minutes of standing); examination of the skin (localized or generalized absence of or excessive sweating, changes in skin temperature or color in the hands and feet) [6].

General laboratory tests should include serum glucose, haemoglobin A1c, thyroid-stimulating hormone, vitamin B12 levels.

Serum and urine protein electrophoresis with immunofixation, including light-chain quantitation, to detect amyloid light-chain amyloidosis; SSA and SSB antibody testing for Sjögren syndrome.

Ganglionic nicotinic α3-AChR autoantibodies, paraneoplastic antibodies (anti-Hu, P/Q and N-type voltage-gated calcium channel and voltage-gated potassium complex antibodies), is indicated in patients with subacute onset of symptoms [33].

Determination of NE, E, and dopamine in the supine position and after 5–10 min of standing may be helpful, but require careful interpretation, as can be affected by concomitant use of drugs or impaired presynaptic NE reuptake [48].

Autonomic function evaluation

Autonomic function evaluation assesses sudomotor, cardiovagal and adrenergic vasomotor functions, and is indicated to:

- detect autonomic failure in patients with parkinsonism or ataxia;
- determine the severity of autonomic failure;
- assess small fibers function in case of peripheral neuropathy or ganglionopathy;
- evaluate patients with orthostatic intolerance;
- evaluate disease progression, and response to medications.

The integrity of central and peripheral sudomotor pathways is assessed through thermoregulatory sweat test. The peripheral sympathetic cholinergic innervation of the sweat glands is evaluated with the quantitative sudomotor axon reflex test (QSART), and the quantitative direct and indirect test of sudomotor function (QDIRT) [49, 50].

Autonomic cardiovascular testing entails the measurement of end-organ response to a physiological provocation. Tests that assess the cardiovagal function, include heart rate variability during deep metronomic breathing (6 cycles/min), and the heart rate response to the Valsalva manoeuvre, or Valsalva ratio [51].

The Valsalva manoeuvre is performed by blowing through a mouthpiece connected to a mercury manometer (40 mmHg) for 15 seconds, under beat-to-beat continuous non-invasive BP measurement and electrocardiogram. BP and heart rate (HR) responses to intrathoracic pressure increase are divided in four phases (Figure 1), and reflects both cardiovagal and sympathetic vasomotor function [52]. The Valsalva Ratio is the ratio of the shortest RR interval (the tachycardia)

during or after phase II of the VM to the longest RR interval (the bradycardia) in phase IV, is the most commonly used marker of parasympathetic function. Pathological HR and BP responses to Valsalva manoeuvre are illustrated in Figure 2.

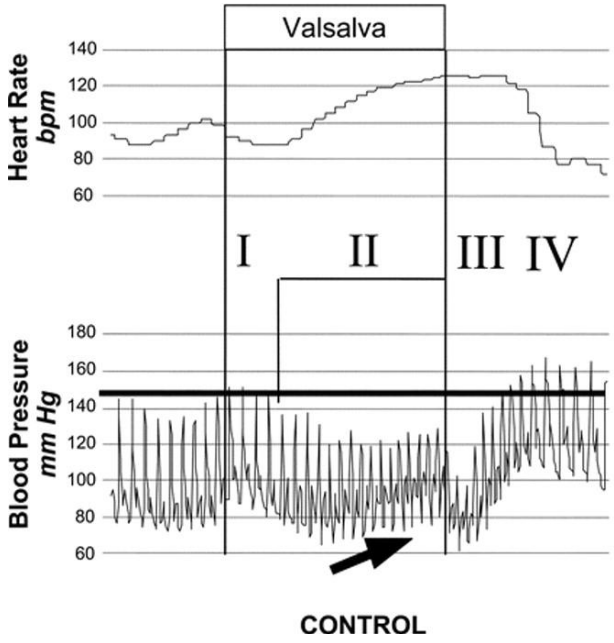

Figure 1: heart rate and blood pressure responses to the Valsalva manoeuvre.

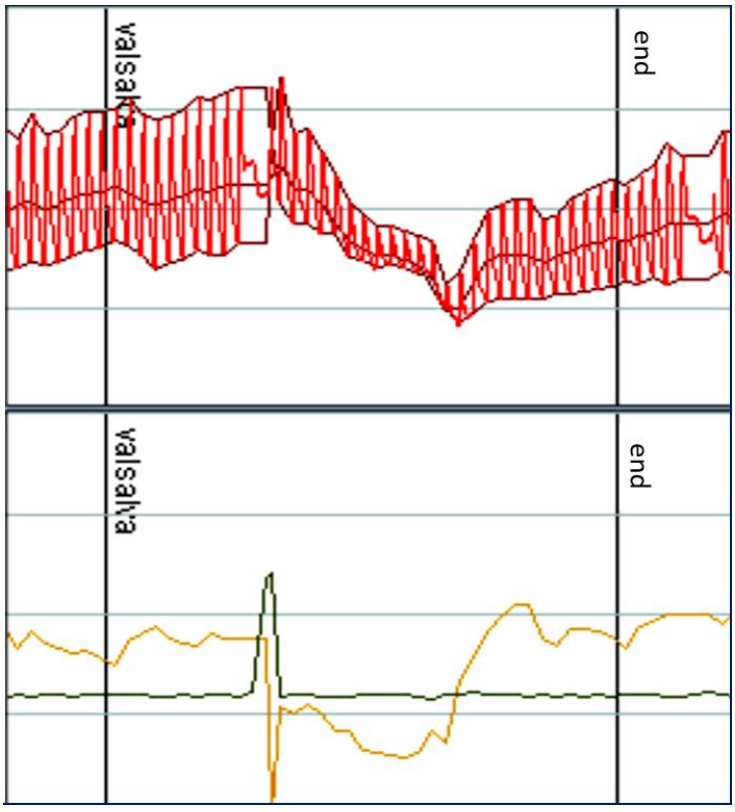

Figure 2: pathologic heart rate and blood pressure responses to Valsalva manoeuvre.

Cardiovagal and sympathetic vasomotor function are also assessed through HR and BP responses to active standing or head-up tilt. The BP response to sustained isometric handgrip contraction for 3 min at 30% of maximum effort, to cold pressor test or to mental arithmetic is a marker for sympatho-excitation, with a quite variable inter-subject response [53].

The baroreflex arch is responsible for the short-term regulation of the cardiovascular system. An increase of BP will be responded by a decrease of HR, and vice versa. To assess the function of the baroreflex arc, baroreflex gain or sensitivity is calculated by measuring the changes of heart rate related to BP changes [54].

24-h ambulatory blood pressure monitoring is a broadly available test, widely used in diagnosis and evaluation of treatment for arterial hypertension. The test gains diagnostic relevance also in patients with dysautonomia, as it is able to detect orthostatic, nocturnal and post-prandial BP variations [55].

Differential diagnosis

Electromyography is indicated for patients with peripheral neuropathy or ganglionopathy, and magnetic resonance imaging (MRI), PET and single-photon emission CT (SPECT), may be helpful in evaluation of central autonomic disorders, in distinguishing between MSA and PD. The presence of atrophy in the putamen, middle cerebellar peduncle and pons on MRI supports the diagnosis of possible MSA [7]. Brain perfusion SPECT shows striatal hypoperfusion in MSA-P, but not in PD [56], and 18F-fluorodeoxyglucose PET shows striatal hypometabolism [57].

Imaging of the postganglionic sympathetic noradrenergic cardiac innervation uses agents that are taken up into sympathetic nerves, and sequestered in storage vesicles within sympathetic neurons. The radiolabeled sympathomimetic amine, 123I-metaiodobenzylguanidine (123I-MIBG), is a substrate for the cell membrane and vesicular NE transporter, and can be imaged with SPECT scanning. MIBG uptake is impaired in PD patients particularly when autonomic failure is present, while these abnormalities are not usually present in MSA patients [58].

Conclusions

As briefly explained, the spectrum of clinical manifestations and disorders associated with autonomic failure is wide and requires a systematic clinical and laboratory approach to establish the diagnosis. A careful history and examination is mandatory, especially in the older patient, coupled with laboratory and other ancillary tests, to search for potentially treatable causes.

Conflict of interest

None

Authors' contribution

All the authors contributed equally to the preparation of the manuscript.

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