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# A retrospective review of autonomic screening tests conducted at a Tertiary General Hospital

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ABSTRACT

Autonomic screening tests (AST) are useful for assessing autonomic dysfunction. Our aim was to delineate the referral pattern, abnormalities, technical difficulties and final diagnoses of ASTs at a Tertiary General Hospital. Referring diagnoses was classified into: orthostatic symptoms, assessment of known/suspected disease associated with dysautonomia, thermoregulatory complaints and neurological disorders. Medication history, patient cooperation and test results were collated. Usefulness of AST in answering the clinical questions was ranked on a 3-point scale. 248 patients were studied. Orthostatic symptoms were the commonest referring diagnosis (71.4%) followed by assessment of a known/suspected disease associated with dysautonomia (13.3%), thermoregulatory complaints (7.7%) and neurological disorders (7.3%). 49.6% of ASTs were abnormal, 40.7% were normal and 9.7% were inconclusive. The first 2 referral categories had the highest proportion of abnormal ASTs while only 5.3% of patients with thermoregulatory complaints had abnormal AST. The most frequent final diagnosis was orthostatic hypotension (OH). It was seen in 31.7% of the cohort; however, 41% of these were attributed to medications. With regard to answering the clinical question, ASTs were very helpful in 56.0% and not helpful in 9.3%. 58.0% of inconclusive ASTs were attributed to poor performance of test maneuvers, 8.0% to medications, 17.0% to both and 17.0% to irregular heart rhythms and pacemakers. 34.7% of patients with diabetes mellitus and 38.2% of patients with Parkinsonism had signs of autonomic dysfunction. About 7% of diabetic and a quarter of Parkinsonism patients had OH secondary to medications. We believe these findings can contribute to better application of AST.



## 1. Introduction

The autonomic nervous system plays an essential role in the regulation of vital physiological functions such as blood pressure, heart rate, thermoregulation, respiration, gastrointestinal activity, bladder control and the sexual response (Low et al., 2013). Therefore, autonomic dysfunction presents as a wide range of symptoms, ranging from orthostatic hypotension (OH) (Shibao et al., 2007; Mustafa et al., 2012) urinary frequency, urgency, incontinence, chronic constipation, sicca, erectile failure to abnormal sweating (Kaufmann and Biaggioni, 2003). These symptoms are however, not specific and can also arise from pathology confined to the various organs, medications as well as functional disorders. Autonomic screening tests (AST) have been widely used in this context to help correctly ascribe pathology to the autonomic nervous system. It defines patterns of abnormality and grades the severity of dysautonomia. It is also useful in characterizing and classifying diseases such as peripheral neuropathy and Parkinsonism (Goldstein et al., 2011; Low et al., 2013); and in some cases, monitoring response to treatment (Korchounov et al., 2005; Sukul et al., 2012). Previous studies have examined the application of AST to specific conditions such as Parkinson's disease (Korchounov et al., 2005), Multiple Systems Atrophy (MSA) (Lipp et al., 2009; Iodice et al., 2012) and Alzheimer's disease (Zakrzewska-Pniewska et al., 2012). However, a general description on the application, case-mix and utility of AST in a hospital cohort has not been done. The primary aims of this study are to delineate the reasons for referral, pattern of abnormalities, problems in test methods and final diagnoses of patients referred for AST at a Tertiary General Hospital. In addition, we analyzed the AST findings in patients with diseases associated with autonomic failure such as diabetes mellitus (DM) and Parkinsonism.

## 2. Material and methods

We undertook a retrospective review of all ASTs done at the Autonomic Function Laboratory at the National Neuroscience Institute, Singapore, from 2010 to 2012. The institutional ethics committee approved the study. Subjects recruited were aged 18 and older with referring diagnosis of autonomic dysfunction or symptoms suggestive of autonomic dysfunction. The following information was collected from the AST database: patient's age and sex, current medications,

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co-morbidities such as DM and Parkinsonism, referring diagnosis, AST results and final diagnoses. Using the information in the AST request forms, we classified the referring diagnosis into 4 broad categories: orthostatic symptoms, assessment of a known/suspected disease associated with dysautonomia, thermoregulatory and neurological disorders (Sukul et al., 2012). Table 1 lists the definition for each of these categories (Table 1).

### 2.1. Autonomic function tests

Parasympathetic system was assessed primarily via evaluation of cardiovagal function. Heart rate variability during standing was assessed using the 30:15 ratio, obtained by dividing RR intervals at the 30th and 15th heartbeats after standing. Respiratory sinus arrhythmia was quantified by calculating the difference between maximum and minimum heart rates during 6 cycles of respiration over a 1-minute interval. The Valsalva ratio was calculated using heart rates at stages II and IV of the Valsalva maneuver. To assess the sympathetic system, the blood pressure response to orthostatic stress (standing as well as passive 60 degree tilt), standardized isometric exercise and cold pressor stimuli was measured. Symptoms of orthostatic hypotension, such as giddiness, were recorded. Sympathetic skin response to cough, deep breaths, loud sound and noxious electrical stimulation was elicited at the palm and sole.

### 2.2. Final diagnoses

Final diagnoses were made after comparing AST parameters against age-adjusted normal values (Christopher and Mathias, 1999). The patient's clinical presentation and medication history were obtained from the referral forms. The patients were said to have sympathetic dysfunction if they had abnormalities in 2 or more sympathetic tests listed above. Parasympathetic dysfunction was concluded if at least 2 of the parasympathetic tests were abnormal. Patients with both sympathetic and parasympathetic abnormalities were given a diagnosis of mixed autonomic dysfunction. A diagnosis of diabetic autonomic neuropathy was made if AST revealed predominantly parasympathetic dysfunction in patients with diabetes mellitus. Postural tachycardia was defined as a rise in heart rate by 30 beats per minute within the first 10 min of posture change and in the absence of OH (Thieben et al., 2007). OH was defined as a decrease in blood pressure of 20 mm Hg systolic and 10 mm Hg diastolic after 2 min of standing or tilt table (Anon., 1996). The diagnosis of OH was only given if there were no other signs of sympathetic or parasympathetic dysfunction. History of using medications known to cause OH was sought (Poon and Braun, 2005).

### 2.3. Clinical utility of AST

The usefulness of AST, that is the ability to answer the clinical question posed by the referring physician, in ruling in or ruling out autonomic dysfunction and in finding an alternative explanation for the patient's symptoms was assessed and graded on a 3-point scale adapted from a previous study (Sukul et al., 2012). We used the criteria listed in Table 2 to score the usefulness of AST as 3, very helpful; 2, somewhat helpful; and 1, not helpful based on information provided in the referral form.

## 3. Results

### 3.1. Test findings

A total of 248 patients underwent AST testing at the Autonomic Function Laboratory from 2010 to 2012. The mean age of patients was 61.8 (range 18–96). About two thirds were males (67.7%). 72 patients had DM and 21 patients had Parkinsonism. Upon classifying the referring diagnoses into broad categories, orthostatic symptoms were the most common (71.4%), followed by assessment of a known/suspected disease associated with dysautonomia (13.3%), thermoregulatory complaints (7.7%) and neurological disorders (7.3%). One patient did not have a referring diagnosis documented (0.4%).

Of the 248 ASTs, 49.6% were abnormal, 40.7% were normal and 9.7% inconclusive (Fig. 1a). Of the abnormal results, the most common final diagnosis was OH, seen in 31.7% of patients (Fig. 1b). 59.0% of these patients had isolated OH, while 41.0% had OH secondary to medication (Fig. 1c). Mixed sympathetic and parasympathetic dysfunctions (29.2%), and diabetic autonomic neuropathy (19.5%) were the next most common final diagnoses (Fig. 1b). Postural tachycardia syndrome (0.8%) and persistently low blood pressure (0.8%) were least common (Fig. 1b).

Patients who were referred for assessment of known/suspected disease and orthostatic symptoms were most likely to have an abnormal AST. 66.7% of patients referred for assessment of a known or suspected disease had an abnormal AST, while 65.5% of patients referred for orthostatic symptoms, 44.4% of those referred for neurological disorders and 5.3% with thermoregulatory complaints had abnormal AST (Fig. 2). Based on the criteria listed in Table 2, AST was found to be very helpful in 56.0%, somewhat helpful in 34.7% and not helpful in 9.3%. Among the 23 inconclusive ASTs, 58.0% were attributed to poor performance of test maneuvers, 8.0% to medications, 17.0% to both and 17.0% to irregular heart rhythms and pacemakers. All 3 patients with irregular heart rhythms and pacemakers had inconclusive results.

### 3.2. Assessment of patients with known/suspected disease associated with dysautonomia

After orthostatic intolerance this was the most frequent referral question. The most common conditions within this category were diabetes mellitus (48.5%), followed by MSA (27.3%), Parkinsonism (12.1%), Sjogren's syndrome (3.0%), amyloid neuropathy (3.0%), Ross syndrome (3.0%) and erythromelalgia (3.0%).

16 patients were referred with a specific diagnosis of diabetic autonomic neuropathy. AST was normal in 5 patients; 4 were diagnosed with diabetic autonomic neuropathy, 2 were with mixed autonomic failure, 1 was with isolated OH, 1 was with OH secondary to medications and 3 were inconclusive. Other DM patients were not referred specifically for diabetic autonomic neuropathy but for other complaints; and were therefore grouped in the other referral-diagnostic categories. Overall, we identified 72 patients with DM. 34.7% of the 72 patients

**Table 1**
Categories of referring diagnoses.

| Orthostatic symptoms | Assessment of a known/suspected disease associated with dysautonomia | Thermoregulatory complaints | Neurological disorders |
|---|---|---|---|
| Orthostatic hypotension | Diabetic autonomic neuropathy | Anhidrosis/hypohidrosis | Autonomic neuropathy |
| Syncope | Parkinsonism | Cold intolerance | Baroreceptor failure |
| Giddiness | Multiple system atrophy | Heat intolerance | Dysautonomia |
| Tachycardia | Amyloid neuropathy | Facial flushing | Sympathetic failure |
| | Sjogren's syndrome | | Vertigo |
| | Erythromelalgia | | Tremor |
| | Ross syndrome | | Headache |