

## SHORT REPORT

## Quantitative cardiovascular autonomic function study in Fisher syndrome

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Quantitative cardiovascular autonomic function tests were performed longitudinally in nine patients with Fisher syndrome (FS). Parasympathetic autonomic function was evaluated by the Valsalva ratio and RR interval variation during rest and deep breathing. Sympathetic autonomic function was evaluated by blood pressure responses to sustained handgrip and to active standing. None of the patients with FS had clinical signs of autonomic dysfunction during the course of their illness. However, autonomic function abnormalities were seen in up to 83% of patients with FS. Thus, bedside clinical signs of autonomic dysfunctions are inadequate for the assessment of autonomic abnormality compared with quantitative autonomic function examination. Most autonomic function tests tended to improve after 4–12 weeks. Although parasympathetic and sympathetic functions were both involved at the height of FS, parasympathetic fibres were less vulnerable than the sympathetic fibres.

Guillain-Barré syndrome (GBS) is an immune mediated inflammatory disease of the peripheral nervous system. The clinical features consist of acute or subacute weakness with areflexia and sensory deficits.<sup>1</sup> Fisher syndrome (FS), after Fisher's classical description,<sup>2</sup> has been recognised as a clinical variant of GBS. It is characterised by the triad of ataxia, areflexia, and ophthalmoplegia.

Autonomic neuropathy is a common and important complication of GBS.<sup>3</sup> Longitudinal autonomic function studies have shown that autonomic dysfunction in GBS is temporary and may improve gradually.<sup>4–6</sup> Autonomic dysfunction occurs only rarely in FS<sup>7,8</sup> and quantitative data concerning cardiovascular autonomic dysfunction in FS are not available. The purpose of this study was to examine cardiovascular function quantitatively and serially in patients with FS and to assess the clinical significance of the function tests.

## PATIENTS AND METHODS

## Patients

Nine patients (five men and four women) with FS were studied. All patients presented with the triad of ataxia, areflexia, and ophthalmoplegia.<sup>2</sup> The mean age of these nine patients was 42.9 years (range 26–65 years, median 43 years). None suffered from hypertension, heart disease, or diabetes mellitus. Four patients had an upper respiratory tract infection at an interval ranging from 1–14 days before the onset of neuropathy. The patients' motor disability was graded on a scale from 0 to 6 modified from Hughes *et al.*,<sup>9</sup> where 0 indicates a normal functional state without neurological deficits; 1, minor symptoms or signs but with the ability to do manual work; 2, ability to walk 5 m or more without assistance; 3, ability to walk 5 m or more with assistance; 4, confinement to a chair or bed; 5, requirement for mechanical ventilation; and 6, death.

Sensory function was graded from 0 to 3 as follows: 0, normal; 1, symptoms but no signs; 2, hypaesthesia or hypalgesia of fingers or feet; and 3, hypaesthesia or hypalgesia to the elbows or knees or worse.<sup>5</sup> The mean evolving time from the onset of neuropathy to the nadir was 3.9 days (range 1–9 days, median 5 days). None of the patients received specific treatment such as plasmapheresis or intravenous immunoglobulin during their illness.

## Controls

To provide an age comparable control group, 23 healthy volunteers, 12 men and 11 women, mean (SD) age 47.7 (12.1) years (range 15–73 years, median 50.0 years) without any signs and symptoms of autonomic dysfunction were studied. Normal values for the Valsalva ratio and RR interval variation (RRIV) were calculated from another 127 normal subjects (mean (SD) age 51.5 (17.6) years, range 16–82 years). None had any medication 24 hours before and during the autonomic testing. All subjects gave their informed consent in this study.

## Autonomic function tests

During the whole procedure, instantaneous heart rate and blood pressure (BP) were measured continuously by means of a Finapres finger BP device connected to an Ohmeda 2300 NIBP monitor (Ohmeda, Englewood, Colorado, USA).<sup>10</sup> All data were digitised and stored immediately in an IBM compatible personal computer for off line analysis. On line review of the results was available during each test to assure a good recording.

Procedures of the autonomic function tests were described previously.<sup>6</sup> The autonomic function tests were the Valsalva ratio, RRIV during rest and deep breathing, and BP responses to sustained handgrip (SH) and active standing. During the Valsalva ratio test, the patient was asked to blow into a mouthpiece and maintain a pressure of about 40 mm Hg for 15 seconds. RRIV measurements were recorded during rest and deep breathing according to the method described by Shahani *et al.*<sup>11</sup> Five groups of 20 sweeps were recorded during rest (rest RRIV) and two groups were recorded during deep breathing at a rate of six breaths/min. RRIV in each group was calculated by the following formula: (longest – shortest RR intervals) / average of 20 RR intervals × 100%. The five rest RRIV and two deep breathing RRIV values were then averaged to obtain the final RRIV during rest and deep breathing, respectively. During the SH test, handgrip was maintained at a third of the maximum voluntary contraction pressure for three minutes or until the subject was exhausted.

The age matched lower limits of normal for the Valsalva ratio were 1.38, 1.33, 1.28, 1.24, 1.20, and 1.16 for subjects

**Abbreviations:** BP, blood pressure; FS, Fisher syndrome; GBS, Guillain-Barré syndrome; RRIV, RR interval variation; SH, sustained handgrip

**Table 1** Percentage of abnormal responses to various autonomic function tests in nine patients with Fisher syndrome

	Criteria of abnormality	Initial (n=9)	4 weeks (n=6)	12 weeks (n=5)	24 weeks (n=5)
VR		44	0	0	0
Rest RRIV		11	17	20	20
DBRRIV		22	17	0	0
SH	≤10 mm Hg	67	83	20	0
BPST	>20 mmHg	22	0	0	0

BPST, blood pressure responses to active standing; DBRRIV, RR interval variation during deep breathing; rest RRIV, RR interval variation during rest; SH, blood pressure response to sustained handgrip; VR, Valsalva ratio.

**Table 2** Results of serial autonomic function tests in nine patients with Fisher syndrome

	Initial (n=9)	4 weeks (n=6)	12 weeks (n=5)	24 weeks (n=5)	Healthy volunteers (n=23)
VR	1.52 (0.46)	1.58 (0.18)	1.67 (0.37)	1.56 (0.22)	1.57 (0.19)
Rest RRIV (%)	10.5 (4.2)*	15.6 (9.1)	16.1 (6.9)	15.9 (11.0)	13.9 (2.7)
DBRRIV (%)	22.4 (8.5)	29.0 (7.3)	36.4 (11.4)	32.0 (6.4)	25.4 (5.6)
SH (mm Hg)	11.3 (10.1)	8.3 (2.3)**	15.8 (9.0)	17.0 (8.7)	15.4 (4.7)
BPST (mm Hg)	16.1 (13.2)**	7.0 (7.3)	-1.3 (4.8)	2.8 (6.9)	5.8 (6.5)

Data are mean (SD). \* $p < 0.05$ ; \*\* $p < 0.01$  compared with healthy volunteers.

aged ≤30, 31–40, 41–50, 51–60, 61–70, and >70 years, respectively. The age matched lower limits of normal for rest RRIV were 10.7%, 8.4%, 6.6%, 5.0%, 3.5%, and 2.9%, and those for deep breathing RRIV were 23.9%, 16.1%, 13.8%, 8.7%, 7.3%, and 4.6% for subjects age ≤30, 31–40, 41–50, 51–60, 61–70, and >70 years, respectively. A Valsalva ratio or RRIV below the age matched lower limit of normal was considered abnormal. In the SH test, a rise of the diastolic BP measured on the contralateral arm of ≤10 mm Hg was considered abnormal.<sup>12</sup> In the test of BP response to active standing, a drop of the systolic pressure of >20 mm Hg was considered abnormal.<sup>10</sup>

The battery of autonomic function tests was performed within several days of hospitalisation and again at 4, 12, and 24 weeks after the onset of neuropathy. The interval between the onset of neuropathy and the initial autonomic function tests in these nine patients ranged from 7–17 days (mean 11.7 days).

### Statistical analysis

Data are expressed as mean (SD) unless otherwise indicated. Differences between disease stage were analysed by a two tailed, unpaired *t* test. Results were considered significant for  $p < 0.05$ .

### RESULTS

At the time of their maximal deficits, five patients were still able to walk without assistance and the other four needed support for ambulation. Motor disability was related primarily to truncal ataxia in these patients. Sensory disturbance was found in six patients. The mean sensory function score of the nine patients was 1.2 (range 0–3, median 1). None had evidence of autonomic dysfunction as tachycardia, bradycardia, fluctuating BP, sphincter disturbance, or abnormal sweating during the course of their illness. All patients had a good recovery (disability score of 0) and the mean recovery time was 131.2 days (range 57–318 days, median 81 days).

Abnormal Valsalva ratio, RRIV during deep breathing, and BP response to active standing were noted within the first month of neuropathy and became normal at subsequent studies. Abnormal RRIV during rest and abnormal BP responses to SH were noted initially and up to 24 weeks after the onset of neuropathy (table 1). Rest RRIV, as well as BP responses to SH and active standing, were significantly lower in FS patients than in healthy subjects within the first month

of illness. All the abnormal autonomic responses tended to improve within 4–12 weeks after the onset of neuropathy (table 2).

### DISCUSSION

Manifestations of autonomic dysfunction in patients with GBS include cardiac arrhythmias, BP fluctuations, sweating disorder, gastrointestinal dysfunction, and sphincter disturbance.<sup>3</sup> Previous studies found that clinically overt cardiovascular autonomic disturbances such as tachycardia, bradycardia, hypotension, hypertension, and fluctuating BP were present in 27–79% of patients with GBS.<sup>5, 8, 12–14</sup> Quantitative autonomic function tests showed autonomic involvement in a considerably higher proportion of patients with GBS, including those with mild disability at the nadir.<sup>5, 6</sup> On the other hand, autonomic dysfunction occurred only rarely in FS. Arai and Yuki<sup>7</sup> reported on a patient with FS who developed profound hypotension during double filtration plasmapheresis. Medication was required to maintain adequate systolic BP for three weeks. In our previous clinical study, one patient with FS developed transient sinus tachycardia and urine retention during the acute stage.<sup>8</sup> In the present study, none of our patients with FS had clinical signs of autonomic dysfunction during the course of their illness. However, autonomic function abnormality was identified in up to 83% of patients with FS. Therefore, autonomic disturbance may occur not only in patients with GBS but also in those with FS. Also, bedside clinical signs of autonomic dysfunctions such as tachycardia, bradycardia, fluctuating BP, and sweating abnormality are inadequate for assessment of autonomic function abnormality compared with quantitative autonomic function examination.

Parasympathetic and sympathetic contributions in the behaviours of various autonomic function tests are variable. Deep breathing RRIV is a specific test for vagal tone<sup>15</sup> and diastolic BP response to SH is used to evaluate sympathetic tone because it correlates well with muscle sympathetic activity.<sup>16</sup> In the present study, the BP responses to SH were significantly lower in patients with FS than in healthy controls. Besides, abnormal results were observed more frequently in the test of BP responses to SH than in the test of deep breathing RRIV in FS. These findings imply that the parasympathetic fibres are less vulnerable than the sympathetic fibres in FS.

Clinical manifestations of FS are unique. Several clinical reports suggested that the cause of FS was a brainstem abnormality alone or in combination with peripheral nerve pathology.<sup>17, 18</sup> On the other hand, many studies<sup>8, 14</sup> have shown that FS and the demyelinating form of GBS share many clinical features, which suggests that FS is a peripheral nerve disorder, as is GBS. In the present study, the preganglionic and postganglionic involvements of the autonomic nervous system were not assessed. Therefore, autonomic dysfunctions observed in FS may be caused by a disorder of the peripheral afferents, central commands of the autonomic system, or both.

Longitudinal autonomic function studies in GBS have shown that autonomic dysfunction was temporary and improved gradually after 2–18 months.<sup>4–6</sup> Autonomic function abnormalities of our patients with FS were highest during the acute stage of neuropathy and improved gradually after 1–3 months. Therefore, autonomic dysfunction in FS is transient and resolves gradually over time, as is seen in GBS.

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