Patterns of Neuropathy and Autonomic Failure in Patients With Amyloidosis

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Abstract

Objective—To define the clinical patterns of peripheral neuropathy and autonomic testing abnormalities in patients with amyloidosis.

Patients and Methods—A retrospective chart review was conducted of 65 patients who had biopsy-proven amyloidosis and autonomic function testing between January 1, 1985, and December 31, 1997, at Mayo Clinic's site in Rochester, MN. Patients were required to have neurologic evaluation, autonomic reflex screening, and tissue confirmation of amyloidosis.

Results—We identified 5 clinical patterns of peripheral neuropathy: (1) generalized autonomic failure and polyneuropathy with pain (40 patients [62%]), (2) generalized autonomic failure and polyneuropathy without pain (11 [17%]), (3) isolated generalized autonomic failure (7 [11%]), (4) polyneuropathy without generalized autonomic failure (4 [6%]), and (5) generalized autonomic failure and small-fiber (ie, autonomic and somatic C-fiber) neuropathy (3 [5%]). Moderately severe generalized autonomic failure, involving adrenergic, cardiovagal, or sudomotor domains, was found in all patients, including those without clinically manifested autonomic failure. The diagnosis of amyloidosis was delayed in patients who did not have initial symptoms of pain or generalized autonomic failure (48 months to diagnosis in patients with polyneuropathy without autonomic failure vs 12 months to diagnosis in patients with autonomic failure and small-fiber neuropathy; *P*=.57).

Conclusion—Physicians should test for symptoms of generalized autonomic failure in patients who have peripheral neuropathy of unknown origin. Autonomic testing may give abnormal results in patients without overt symptoms of autonomic failure. Early recognition of autonomic failure may lead to earlier diagnosis of the underlying pathogenesis of amyloidosis, as well as earlier treatment for patients with this condition.

Although autonomic failure and peripheral neuropathy result in some of the earliest and most disabling symptoms experienced by patients with amyloidosis,[1-7] only limited information is available about the patterns of clinical autonomic neuropathic symptoms and autonomic laboratory test abnormalities in these patients. The term *autonomic neuropathy* has often been used interchangeably with *orthostatic hypotension*,[1,8] and many early descriptions of peripheral neuropathy in patients with amyloidosis[6,8,9] did not indicate whether the patients

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had other symptoms of autonomic failure, such as diarrhea, sweating abnormalities, impotence, or urinary symptoms.

Research has led to improved understanding of autonomic failure, particularly with the standardization of testing and scores. The extent and severity of autonomic failure can be quantified by using the components of the autonomic reflex screen (ARS), a battery of autonomic tests used to evaluate adrenergic, cardiovagal, and sudomotor function. Results of these tests can then be used to calculate the composite autonomic severity score (CASS), which corrects for the confounding effects of age and sex.[10]

We review the clinical patterns of peripheral neuropathy in a large group of patients with amyloidosis and quantify the severity and distribution of autonomic failure in these patients by using the ARS and CASS.

Patients and Methods

A retrospective chart review was conducted of patients who had been diagnosed as having biopsy-proven amyloidosis and who had autonomic testing performed between January 1, 1985, and December 31, 1997, at Mayo Clinic's site in Rochester, MN. Sixty-five patients, with a median age of 63 years (interquartile range [IQR], 32-79 years), were included. Twenty (31%) of the patients were women. The diagnosis of amyloidosis was made through biopsy of nerve, fat, skin, kidney, liver, stomach, colon, or flexor retinaculum tissue. Patterns of autonomic failure and polyneuropathy, ARS results, and CASS were tabulated for these patients. The Mayo Clinic Institutional Review Board approved all aspects of the current study.

Definitions

The term *autonomic failure* was used to encompass the widespread abnormalities of the autonomic nervous system seen in patients with amyloidosis. Symptoms of autonomic failure included the following[11,12]: pupillary (symptoms of blurred vision or problems with glare resulting from impaired parasympathetic pupillary activity), secretomotor (dry eyes or dry mouth resulting from impaired cholinergic sympathetic innervation to lacrimal or salivary glands, or abnormal sudomotor function, including gustatory sweating and heat intolerance), vasomotor (excessively cold hands and cold feet with discoloration resulting from peripheral adrenergic sympathetic dysfunction), orthostatic intolerance (light-headedness, dizziness, or dull neck or shoulder aching resulting from confirmed orthostatic hypotension), gastrointestinal (symptoms of nausea, vomiting, bloating, early satiety, abdominal colic, incontinence, or alternating diarrhea and obstinate constipation), genitourinary (urinary frequency and urgency, incontinence, or increased residual urinary retention), and sexual dysfunction (difficulty with erection and ejaculation).

Patients were characterized as having either peripheral neuropathy or isolated small-fiber neuropathy. *Polyneuropathy* (with or without pain) was defined as length-dependent weakness and loss of vibration or sensation, with, at a minimum, loss of ankle reflexes on examination. *Small-fiber neuropathy* was defined as symptoms of prominent pain and burning in the feet and/or hands, with distal loss of pain and temperature sensation and relative preservation of distal vibration sensation and reflexes on examination.[13]

Five clinical patterns of generalized autonomic failure (GAF) and peripheral neuropathy were recorded: (1) GAF and polyneuropathy with pain, involving large fibers and small fibers (ie, autonomic and somatic C fibers); (2) GAF and polyneuropathy without pain, involving large fibers and autonomic fibers; (3) GAF only, involving autonomic fibers alone; (4) polyneuropathy without GAF, involving large somatic fibers alone; and (5) GAF and small-fiber neuropathy, involving small fibers (ie, autonomic and somatic C fibers).

Tests of Autonomic Function

The ARS was used to measure adrenergic, cardiovagal, and sudomotor function. The ARS consists of a battery of previously described tests,[11] including the quantitative sudomotor axon reflex test (QSART), the heart rate response to deep breathing test, the Valsalva maneuver, and the blood pressure and heart rate response to tilt test.

The QSART was used to measure postganglionic sympathetic sudomotor function from 1 upper extremity and 3 lower extremity sites. The heart rate response to deep breathing, at a rate of 6 breaths/min, was used to evaluate cardiovagal function. The Valsalva ratio, another measure of cardiovagal function, was calculated from the maximal and minimal heart rates obtained in the Valsalva maneuver. The blood pressure and heart rate response to tilt, after 1 and 5 minutes in the upright position, as well as the beat-to-beat blood pressure response to the Valsalva maneuver, were used to evaluate adrenergic function.

The adrenergic, cardiovagal, and sudomotor components of the ARS were reported using the CASS,[10] which provided an assessment of the severity of autonomic failure. Each component was assigned a score in the following ranges: adrenergic CASS (0-4), cardiovagal CASS (0-3), and sudomotor CASS (0-3). The total CASS (range 0-10) was calculated from the sum of the individual components. Individual scores were graded so that a total CASS from 1 to 3 represented mild autonomic failure; a total CASS from 4 to 6, moderate autonomic failure; and a total CASS from 7 to 10, severe autonomic failure.[10]

Statistical Analyses

Summary statistics were presented as median and IQR. Group comparisons were made using the 2-sided Wilcoxon rank sum tests. Ordinal data were compared using the Wilcoxon signed rank test. $P<.05$ was considered significant unless otherwise stated.

Results

Of the 65 patients included in the chart review, 43 (66%) were diagnosed as having systemic light-chain amyloidosis using serum or urine immunofixation electrophoresis, and 22 (34%) were diagnosed as having familial amyloid polyneuropathy (FAP) through the use of genetic testing.

One patient with FAP was found to have the gelsolin (amyloidosis, Finnish type) (*GSN*) sequence variation and an IGA-κ monoclonal gammopathy. One patient with systemic amyloidosis had a low vitamin B_{12} level; however, amyloidosis symptoms progressed in this patient despite vitamin B_{12} replacement therapy. No other obvious causes of peripheral or autonomic neuropathy (such as diabetes mellitus) were identified in any of the patients.

In patients who were initially found to have a monoclonal gammopathy, the mean latency period between the detection of the monoclonal gammopathy and the diagnosis of systemic amyloidosis was 7 months (IQR, 3-72 months). The median time to diagnosis after symptom onset was 24 months (IQR, 3-384 months) for all patients. The only significant difference between patients with systemic light-chain amyloidosis and patients with FAP was median time to diagnosis (18 months [IQR, 3-156 months] in patients with systemic light-chain amyloidosis vs 36 months [IQR, 12-384 months] in patients with FAP; $P<.001$).

Electromyography (EMG) was performed at Mayo Clinic's site in Rochester, MN for 52 patients (80%). Evidence of axonal sensorimotor polyneuropathies was found in 49 (94%) of the 52 patients who had EMGs recorded. The EMGs of 3 patients did not reveal evidence of sensorimotor polyneuropathies: results were normal in 1 patient with isolated autonomic failure; the EMG revealed evidence of lumbosacral radiculopathy in 1 patient with both

autonomic and neuropathic symptoms; and the EMG revealed evidence of a median neuropathy across the wrist (ie, carpal tunnel syndrome) in a patient who was eventually diagnosed as having FAP.

Autonomic Symptoms

The autonomic symptoms are summarized in Table 1. The most common symptom was orthostatic intolerance (in 48 patients [74%]), followed by gastrointestinal (46 [71%]) and secretomotor (35 [54%]) symptoms. Other symptoms included genitourinary, vasomotor, and pupillary. Four patients (6%) were recorded as having no autonomic symptoms.

Neuropathy Patterns

The number (percentage) of patients with each of the 5 clinical patterns of neuropathic involvement (as described in the "Definitions" section), along with median times to diagnosis, is shown in Table 2. The patient with the *GSN* sequence variation was diagnosed as having pattern 2 at 384 months after symptom onset.

Comparing patients diagnosed as having pattern 4 (ie, those without GAF) with patients diagnosed as having pattern 5 (ie, those with GAF and small-fiber neuropathy), the time to diagnosis appeared to be delayed (48 vs 12 months; *P*=.57; Wilcoxon signed rank test). This result reflects the small sample size of the study population.

Tests of Autonomic Function

The CASS results that were calculated are shown in Table 3. Results for 1 or more components of the ARS (ie, adrenergic, cardiovagal, sudomotor) were abnormal in all patients, including the 4 patients without autonomic symptoms. The median total CASS was calculated for 58 (89%) of the 65 patients. One patient did not have QSART results because of distal edema, and 6 patients had arrhythmias or pacemakers that interfered with interpretation of the cardiovagal response to deep breathing and the Valsalva maneuver.

The median total CASS was 7 (range 0-10); the median adrenergic CASS was 3 (range, 0-4); the median cardiovagal CASS was 3 (range, 0-3); and the median sudomotor CASS was 2 (range, 0-3). The ranges of the individual CASS results include 0, indicating that results of individual ARS components of testing were normal in some patients.

Discussion

Our study shows the existence of 5 clinical patterns of peripheral neuropathy in patients with amyloidosis, indicating that the severity of autonomic testing abnormalities is generally moderate in these patients. Although symptoms related to orthostatic hypotension and gastrointestinal problems have previously been reported as commonly encountered in patients with amyloidosis,[2,7,14-16] the current study shows that secretomotor symptoms (eg, dry eyes, dry mouth) and sweating abnormalities may also be common.

The shortest time to diagnosis was found in patients with pattern 5 (GAF and small-fiber neuropathy); however, the median time to diagnosis in this group was still rather long, at 12 months. The longest time to diagnosis, 48 months, was found in patients with pattern 4 (polyneuropathy without GAF). Eleven patients (17%) had GAF and polyneuropathy without pain (pattern 2), whereas 4 patients (6%) had polyneuropathy without GAF (pattern 4). Interestingly, the presence of autonomic failure alone (pattern 3) did not lead to earlier diagnosis of amyloidosis. The median time to diagnosis in patients with pattern 3 was 24 months.

The distribution by pattern category in this patient population is instructive. Pattern 1 (GAF and polyneuropathy with pain) affected almost 2 in 3 patients (62%), whereas pattern 4 (polyneuropathy without GAF) affected only 6% of patients. Of note, symptoms of GAF affected 94% of the patients.

Overlooking symptoms of autonomic failure can lead to the underrecognition of peripheral neuropathies associated with GAF. Previous reports[7,17-20] have clearly demonstrated that the diagnosis of amyloidosis is delayed when the characteristic presentation of amyloidosis[4,7,21] (ie, a progressive sensorimotor polyneuropathy with predominant pain and autonomic dysfunction) is absent.

Minimal information is available on results of autonomic function testing in patients with amyloidosis. Evaluation of autonomic function in such patients is typically confined to the presence or absence of orthostatic hypotension.[1] Studies involving small numbers of patients have suggested that autonomic function abnormalities are present in most patients with amyloid neuropathy. These studies include examinations of heart rate variability in time[15] and frequency.[22] Abnormalities have also been reported in tests of adrenergic function, including head-up tilt, mental arithmetic,[23] skin vasomotor reflexes, and pressor responses to cutaneous cold.[24]

The current study is limited by its retrospective nature. Symptoms of peripheral neuropathy and autonomic failure were derived from clinical records, which are biased by patient recall and examiner questions. Uniform questionnaires were not used, limiting the ability to make correlations between symptoms and testing. The degree of neurologic disability and the severity of symptoms could not be ascertained. From the information available, we determined that only 1 of the 13 patients without orthostatic hypotension had normal autonomic functioning. In each of the 4 asymptomatic patients, at least 1 component of the ARS was abnormal.

Some previous studies have attempted to quantify the severity of symptoms in patients with amyloidosis by using scores for normal (0), borderline (1), and abnormal (2).[25-27] Other studies have used a scoring system ranging from 0 (symptoms absent) to 6 (eg, severe diarrhea or permanent incontinence)[28] or a visual analog scale ranging from 0 (symptoms never experienced) to 100 (symptoms always experienced).[29] However, the frequency, aggravators, and alleviators of symptoms could not be measured using these systems.

The severity and progression of disease, as well as the effect on patients' quality of life, could not be assessed in the current study. A standardized and validated questionnaire covering symptoms of autonomic failure (ie, male sexual dysfunction and orthostatic, secretomotor, sudomotor, urinary, gastrointestinal, pupillomotor, and vasomotor symptoms) has since been developed to evaluate symptom severity, progression, frequency, aggravators, and alleviators. [30] This questionnaire can be used to address quality-of-life measures in patients.

Because of these limitations, we anchored our study around the ARS and CASS, so that the ARS could be performed with all patients.

Conclusion

The different patterns of peripheral neuropathy and autonomic testing abnormalities documented in the current study provide clinical insights for treating patients with amyloidosis. The absence of overt symptoms of autonomic failure can lead to delay in diagnosis of amyloidosis. We have shown that polyneuropathy in patients with either systemic or familial amyloidosis can occur without autonomic symptoms or pain. Polyneuropathy may be the earliest symptom of amyloidosis, and there is often a lag between symptom onset and the

development of autonomic symptoms. Screening for autonomic symptoms in patients with polyneuropathy narrows the differential diagnosis to the few disorders of autonomic failure or to peripheral neuropathy with autonomic failure.

Autonomic testing may yield abnormal results before clinical autonomic symptoms begin. Thus, when available, testing for autonomic failure may be helpful in cases in which the diagnosis is unclear. A battery of autonomic tests is likely to be most useful because abnormalities of adrenergic, cardiovagal, or sudomotor function may be heterogeneous, especially early in the disease process. Early detection of amyloidosis and early recognition of autonomic failure will allow for earlier treatment intervention in affected patients.

Acknowledgments

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Glossary

ARS	autonomic reflex screen
CASS	composite autonomic severity score
EMG	electromyography
FAP	familial amyloid polyneuropathy
GAF	generalized autonomic failure
IQR	interquartile range
QSART	quantitative sudomotor axon reflex test

TABLE 1
Summary of Autonomic Symptoms in 65 Patients With Amyloidosis

Symptom	No. (%) of patients
Orthostatic intolerance	48 (74)
Gastrointestinal	46 (71)
Secretomotor	35 (54)
Genitourinary	25 (39)
Erectile dysfunction[a]	30 (67)
Vasomotor	17 (26)
Pupillary	16 (25)
None	4 (6)

[a]N = 45; male patients only.

TABLE 2

Patterns of Generalized Autonomic Failure and Peripheral Neuropathy in 65 Patients With Amyloidosis[a]

Pattern	Description	No. (%) of patients	Time to diagnosis (mo), median (IQR)
1	GAF and polyneuropathy with pain	40 (62)	25 (8-156)
2	GAF and polyneuropathy without pain	11 (17)	16 (3-384)
3	GAF only	7 (11)	24 (6-29)
4	Polyneuropathy without GAF	4 (6)	48 (36-60)[b]
5	GAF and small-fiber neuropathy	3 (5)	12 (6-24)[b]

[a] GAF = generalized autonomic failure; IQR = interquartile range.

[b] $P=.57$.

TABLE 3
Composite Autonomic Severity Scores for 65 Patients With Amyloidosis[a]

ARS component (CASS range)	Median score	No. (%) of patients
Adrenergic (0-4)	3	59 (91)
Cardiovagal (0-3)	3	59 (91)
Sudomotor (0-3)	2	64 (99)
Total (0-10)	7	58 (89)[b]

[a] ARS = autonomic reflex screen; CASS = composite autonomic severity score.

[b] The median total CASS was calculated for 58 of 65 patients. One patient did not have quantitative sudomotor axon reflex test results because of distal edema, and 6 patients had arrhythmias or pacemakers that interfered with interpretation of the cardiovagal response to deep breathing and the Valsalva maneuver.