Orthostatic Hypotension as a Clue to Primary Systemic Amyloidosis

By ROBERT A. KYLE, M.D., BRUCE A. KOTTKE, M.D., AND ALEXANDER SCHIRGER, M.D.

ALTHOUGH HYPOTENSION has been mentioned commonly in primary amyloidosis,\(^1\)\(^-\)\(^3\) reports of orthostatic hypotension have been infrequent.\(^4\)\(^-\)\(^7\) Extensive reviews of syncope or fainting do not mention primary amyloidosis as a possible cause.\(^8\)\(^,\)\(^9\) We have been impressed with the presence of orthostatic hypotension in amyloidosis and have reviewed our experience in this regard.

Methods

We reviewed the records of 138 patients with primary systemic amyloidosis seen at the Mayo Clinic from 1935 through 1964. In all instances, the presence of amyloidosis was proved by tissue biopsy or postmortem examination. The criteria for the diagnosis of orthostatic hypotension included a decrease in the standing blood pressure from the recumbent blood pressure of 30 mm Hg systolic and 20 mm Hg diastolic and the presence of light-headedness or syncope. Our patients were not taking drugs associated with hypotension, had not had surgical sympathectomy, and had no known diabetes mellitus or any other conditions reported to cause orthostatic hypotension. Amyloidosis was considered to be the cause of the orthostatic hypotension in all cases.

Results (Table 1)

Eleven of the 138 patients with primary systemic amyloidosis fulfill the criteria of orthostatic hypotension and constitute the material for this report. In addition, 26 other patients had systolic blood pressures of less than 100 mm Hg, but either there was no evidence of orthostatic hypotension or the information was insufficient to make an unequivocal diagnosis of orthostatic hypotension. Nine of the 11 patients were males, a greater predominance than was our general experience with primary systemic amyloidosis.

None of the patients had a family history suggestive of amyloidosis, evidence of multiple myeloma, or any other underlying disease that might be associated with amyloidosis.

The presenting complaint in three of the 11 patients was related to orthostatic hypotension and consisted of light-headedness, dizziness, syncope, or loss of consciousness. These symptoms tended to worsen as the disease progressed. During the course of their illness, most of the remaining patients had syncope or their activities were significantly hampered by dizziness or light-headedness. Three of the patients were unable to stand or walk at all because of syncope and thus were severely incapacitated. Four of the 11 patients had systolic blood pressure of 120 mm Hg or more when recumbent. One patient had markedly increased hypotension after successful treatment of edema with thiazides, and another patient did not have symptoms of orthostatic hypotension until edema secondary to a nephrotic syndrome was successfully treated with thiazides and spironolactone. This suggests the importance of shifts in body fluid. Symptoms of orthostatic hypotension preceded the diagnosis of amyloidosis in all patients in this series. In fact, symptoms of orthostatic hypotension antedated the diagnosis of amyloidosis by 6 months or more in eight of the 11 patients.

Diarrhea was a symptom in seven of the 11 patients, and steatorrhea was found in two patients and was strongly suspected in one. The incidence of diarrhea was much higher in this group than it was in the patients with primary amyloidosis without orthostatic hypotension (11 of 127 patients, 8.7%), possibly reflecting visceral neuropathy. Orthostatic hypotension...
hypotension preceded the onset of diarrhea in five of the seven patients.

Impotence or decrease in libido was prominent in only two patients. It is likely that this would have been found more often if these symptoms had been sought. Two patients presented with an anorexia nervosa-like syndrome, whereas four others had frequent vomiting. Not surprisingly, loss of weight was a prominent feature and ranged from 15 to 100 lb in eight of 11 patients.

A nephrotic syndrome was present in two patients and strongly suspected in two others in whom incomplete studies were performed. The fact that no patients in this group had congestive heart failure or the clinical features of multiple myeloma was rather unusual.

The physical findings, aside from orthostatic hypotension, were not different from the usual ones in primary amyloidosis.

Anemia had no part in the orthostatic hypotension or syncope, because the hemoglobin value was never less than 10.5 g/100 ml of blood. Significant azotemia (urea value of more than 125 mg) was found in three patients, while three others had slightly elevated concentrations of urea (50 to 70 mg/100 ml of blood). Values for blood urea at the upper limits of normal have been reported in orthostatic hypotension.10 Serum electrophoresis was performed on nine patients. The albumin level was less than 1.9 g/100 ml of serum in four patients and more than 3.0 g in three. Four patients had hypogammaglobulinemia (γ-globulin value of 0.70 g or less/100 ml of serum). One patient had a γ-globulin concentration of 1.43 g/100 ml of serum, and this was distributed in a homogeneous spike.

Although only one patient complained of decreased sweating, this was found in all

### Table 1

Findings in Eleven Cases of Primary Amyloidosis and Orthostatic Hypotension

<table>
<thead>
<tr>
<th>Case</th>
<th>Blood pressure (systolic diastolic) mm Hg</th>
<th>Recumbent</th>
<th>Standing*</th>
<th>Syncope*</th>
<th>Diarrhea*</th>
<th>Nephrotic syndrome*</th>
<th>Peripheral neuropathy*</th>
<th>Onset of orthostatic hypotension</th>
<th>Diagnosis of amyloidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120/70</td>
<td>60</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td></td>
<td>Dec. 1961</td>
<td>June 1962</td>
</tr>
<tr>
<td>2</td>
<td>120/80</td>
<td>80</td>
<td>S</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td></td>
<td>Mar. 1955</td>
<td>Apr. 1956</td>
</tr>
<tr>
<td>3</td>
<td>78/60</td>
<td>44</td>
<td>?</td>
<td>+</td>
<td>0</td>
<td>S</td>
<td>0</td>
<td>Sept. 1961</td>
<td>Nov. 1961</td>
</tr>
<tr>
<td>4</td>
<td>96/64</td>
<td>44</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td></td>
<td>Jan. 1950</td>
<td>Aug. 1962</td>
</tr>
<tr>
<td>5</td>
<td>90/?</td>
<td>50</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td></td>
<td>May 1960</td>
<td>Feb. 1961</td>
</tr>
<tr>
<td>6</td>
<td>124/84</td>
<td>60</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td></td>
<td>July 1952</td>
<td>Mar. 1953</td>
</tr>
<tr>
<td>7</td>
<td>88/70</td>
<td>45</td>
<td>+</td>
<td>0</td>
<td>S</td>
<td>0</td>
<td></td>
<td>Dec. 1951</td>
<td>Jan. 1952</td>
</tr>
<tr>
<td>8</td>
<td>100/70</td>
<td>50</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>1958</td>
<td>Aug. 1959</td>
</tr>
<tr>
<td>9</td>
<td>134/100</td>
<td>84</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td></td>
<td>July 1958</td>
<td>Aug. 1958</td>
</tr>
<tr>
<td>10</td>
<td>100/65</td>
<td>50</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td></td>
<td>1961</td>
<td>June 1964</td>
</tr>
<tr>
<td>11</td>
<td>80/60</td>
<td>30</td>
<td>S</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td></td>
<td>Mar. 1964</td>
<td>Sept. 1964</td>
</tr>
</tbody>
</table>

* + = present; 0 = absent; ? = not recorded; S = suspected but inadequate data.
six patients in whom a sweating test was performed. There was no correlation between the results of the sweating test and the severity of orthostatic hypotension. The patchy type of distribution and lack of correlation are also seen in idiopathic hypotension. Peripheral neuropathy was found in two patients.

Postmortem examination was done in two of our patients. In one patient, amyloid deposits were found in the nerve bundles in both autonomic and peripheral nerves. These deposits distorted and compressed the nerves. In the second patient, large amounts of amyloid were present in the walls of blood vessels within the sciatic nerve as well as in the perineurium of the nerve.

The drug 9α-fluorohydrocortisone, fludrocortisone (Florinef), was used in treatment of four patients. One patient responded well for a year but then became refractory to the drug. Another obtained excellent control of hypotension with this drug and was continuing to do well after 8 months of therapy. One patient had some benefit initially, but the follow-up was inadequate. Another patient obtained no benefit in spite of a large dose of Florinef.

**Discussion**

Orthostatic hypotension probably was first mentioned by Piorry in 1826, but Bradbury and Eggleston presented the first definite delineation of the condition nearly 100 years later. The latter emphasized the triad of low blood pressure on standing, impotence, and anhidrosis. They stated that a compensatory increase in heart rate did not occur with the decrease in blood pressure.

Weakness and fatigue as well as impotence and urinary incontinence frequently are the initial symptoms of orthostatic hypotension. Not uncommonly, the patient experiences light-headedness and fainting when standing. Prolonged syncope can produce convulsive seizures.

Orthostatic hypotension may be idiopathic or it may be secondary to an underlying disease such as diabetes mellitus, Addison’s disease, surgical sympathectomy, prolonged recumbency, pregnancy, inadequate postural reflex, hypotensive or tranquilizing drugs, hypovolemia from anemia or dehydration, hypokalemia, Guillain-Barré syndrome and other peripheral neuropathies, parkinsonism, tabes dorsalis, parasellar tumors, syringomyelia, transection of spinal cord, cerebrovascular insufficiency, encephalomalacia, abnormalities of the autonomic nervous system, and cachexia as well as amyloidosis. Excellent references to these may be found in the reviews by Wagner, Engel, and Schirger and associates.

Although the cause of idiopathic orthostatic hypotension is unknown, the basic disturbance is an autonomic dysfunction which results in decreased arteriolar constriction when standing. However, the excellent observation of Shy and Drager and the clinical observations of members of our group are suggestive of a more generalized process involving the central as well as the autonomic nervous system. Further evidence in this regard was recently presented.

The treatment of orthostatic hypotension generally has been unsatisfactory. Elevation of the head of the bed, wrapping of the legs with elastic bandages, use of abdominal binders, and a high intake of salt have been of benefit in some instances. Ephedrin, desoxy-cortisone acetate, and more recently Florinef have shown promise.

Hypotension is a common finding in primary amyloidosis, and its incidence ranged from 11.8 to 44.0% in a large series of primary amyloidosis. Orthostatic hypotension in primary amyloidosis is much less common, and only a few cases have been reported in the literature. Schneckloth and Page in 1955 reported on a patient with orthostatic hypotension who had a nephrotic syndrome and primary amyloidosis. Four years later Wagner, in a review of orthostatic hypotension, presented a patient with a nephrotic syndrome and orthostatic hypotension secondary to primary amyloidosis. Two cases of polyneuropathy and primary amyloidosis were described by Munsat and Poussaint. Liske and associates reported on a patient with
primary amyloidosis and orthostatic hypotension. In addition Ellis and Haynes, in 1936, reported on a patient with orthostatic hypotension who, at postmortem examination, had amyloidosis of the adrenal glands and spleen. The small abscesses found in the renal cortex probably were not responsible for the amyloidosis. Although this patient probably had primary amyloidosis, Addison's disease cannot be excluded. Weakness, diarrhea, and loss of weight are consistent with either primary systemic amyloidosis or Addison's disease.

Primary systemic amyloidosis has been recognized for more than 100 years, and although the clinical and laboratory findings may be striking, the diagnosis is frequently overlooked. Weakness, fatigue, ankle edema, dyspnea, purpura, and loss of weight are the commonest presenting complaints. Less common but more suggestive of amyloidosis are periorbital purpura, macroglossia, and bilateral paresthesias of the hands (carpal tunnel syndrome). Splenomegaly is uncommon but hepatomegaly is seen in more than 50% of the patients. Submaxillary lymphadenopathy, usually associated with macroglossia, may be a prominent feature. The presence of refractory, congestive heart failure, or a nephrotic syndrome should alert the physician to the possibility of amyloidosis. Steatorrhea is uncommon but may be a significant feature. Laboratory abnormalities including proteinuria or Bence Jones proteinuria, elevation of erythrocyte sedimentation rate and blood urea, and increased sulfobromophthalein-dye retention are common. Electrophoresis of the serum usually reveals hypoalbuminemia and frequently normal or decreased amounts of gamma-globulin. In some instances, a homogeneous serum-protein peak indistinguishable from that of myeloma is found. Plasma cells in the marrow vary from a few mature cells to many immature, atypical cells consistent with multiple myeloma.

Although these findings may be suggestive of primary amyloidosis, an unequivocal diagnosis must be obtained from tissue analysis at antemortem biopsy or postmortem examination. The liver and kidney have been preferred sites for biopsy, but the risk of bleeding and the need for cooperation of the patient and an experienced physician make these sites less than ideal for study. Peroral biopsy of the small bowel is a useful procedure; but tissue cannot always be obtained, and the procedure is uncomfortable for the patient. If involved with amyloid, biopsy specimens of the skin, lymph nodes, muscle, gum, or tongue will confirm the diagnosis. Rectal biopsy appears to be the procedure of choice in the diagnosis of primary amyloidosis.

Bone-marrow aspiration also may be helpful. The mechanism of primary amyloidosis in causing orthostatic hypotension is not clear. In some patients, amyloid deposits within the nerve, causing compression-neuropathy, could be responsible. Ischemia from deposition of amyloid in the walls of the blood vessels supplying the nerves may have a significant part. Both of these possibilities are supported by our findings. The possibility of a toxic or metabolic factor has been postulated. In addition, the involvement of the heart and blood vessels with amyloid might play some role. The small blood vessels involved with amyloid may not be able to respond normally.

In six of 11 patients in our series, Addison's disease was seriously considered in the differential diagnosis. The presence of weakness and fatigue, nausea, vomiting, diarrhea, loss of weight, and hypotension all contributed to the clinical impression of adrenal insufficiency. Adequate metabolic studies excluded Addison's disease in each instance.

Although orthostatic hypotension is an uncommon feature of primary amyloidosis (11 of 138 cases, 8.0%) and the incidence of primary systemic amyloidosis in orthostatic hypotension is even less (five of 384 cases, 1.3%), the association of these two uncommon entities appears greater than a chance relationship. In addition, the incidence of amyloidosis in these patients with orthostatic hypotension may be even greater because the possibility of amyloidosis was not entertained in all instances. Although recumbent blood
pressure may be normal, the physician should look for orthostatic hypotension because four of our patients had a recumbent blood pressure of 120/70 mm or greater. In our series, orthostatic hypotension was diagnosed 3 years before amyloidosis was found in one patient. Thus, the possibility of amyloidosis should be considered in the differential diagnosis of any patient with idiopathic orthostatic hypotension.

Summary

Data on 11 patients with orthostatic hypotension and primary systemic amyloidosis have been presented. Dizziness and light-headedness or syncope significantly hampered the involved patients. Three were incapacitated by orthostatic hypotension.

Diarrhea, nausea, vomiting, and loss of weight were common, and adrenal insufficiency was seriously considered in the differential diagnosis of six of the 11 patients. Abnormal sweating was found in all six in whom this test was done.

The drug 9-α-fluorohydrocortisone showed promise in symptomatic therapy of the condition.

The possibility of primary systemic amyloidosis should be considered in the presence of orthostatic hypotension. Rectal biopsy and bone-marrow aspiration are recommended as initial biopsy procedures unless another organ suitable for biopsy is obviously involved.

References


Centennial Second Edition of Thomas Peacock's 
Malformations of the Human Heart

Orthostatic Hypotension as a Clue to Primary Systemic Amyloidosis
ROBERT A. KYLE, BRUCE A. KOTTKE and ALEXANDER SCHIRGER

Circulation. 1966;34:883-888
doi: 10.1161/01.CIR.34.5.883

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/34/5/883

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/