Decreased serum apolipoprotein AII/AI ratio in systemic amyloidosis

Toshiyuki Yamada, Tetsuo Ozawa, Fumitake Gejyo, Yasuaki Okuda, Kiyoshi Takasugi, Osamu Hotta, Yoshihisa Itoh

Abstract

Objective—To investigate if serum apolipoprotein A-I and A-II (apoAI and apoAII) concentrations change in subjects with systemic amyloidosis secondary to underlying disorders.

Methods—Serum concentrations of apoAI and apoAII were measured in 21 multiple myeloma patients, including eight with amyloidosis; 95 rheumatoid arthritis patients, including 45 with amyloidosis; and 73 haemodialysis patients, including 32 with amyloidosis.

Results—ApoAII values tended to be reduced in subjects with amyloidosis in each group, but could not effectively distinguish amyloidosis. However, apoAII/AI ratios were significantly lower in subjects with amyloidosis in all groups. The ratio of 0.2 had diagnostic sensitivity and specificity for amyloidosis: 50% and 100%, respectively, in multiple myeloma; 80% and 78%, respectively, in rheumatoid arthritis; and 46% and 90%, respectively, in patients requiring long term haemodialysis.

Conclusion—The apoAII/AI ratio can be a useful biochemical marker of suspect amyloidosis in patients with underlying diseases, especially those with rheumatoid arthritis.

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Amyloidosis is a condition in which insoluble fibrillar deposits occupy extracellular spaces and lead to organ dysfunction. There are several types of amyloidosis in terms of clinical features and the protein components that form the amyloid fibrils. Among these are types that are associated with underlying diseases, such as multiple myeloma and rheumatoid arthritis (RA) and in those conditions requiring long term haemodialysis. The involvement of amyloidosis worsens the prognosis of the original disease. The presence of amyloid deposits can be suspected by symptoms like diarrhoea in RA. However, some have poor clinical manifestation among patients with amyloid deposits confirmed by histological examination. As a non-invasive method, scintigraphy, using a labelled serum amyloid P component, has been proved useful, but not easy to perform. Therefore, a simple biochemical test would be helpful to detect the presence of amyloid deposits.

Recently, reduction in serum apolipoprotein AII (apoAII) concentrations has been reported in patients with familial amyloidotic polyneuropathy, which is caused by a mutation in the transthyretin gene. Of importance, subjects with the abnormal gene do not have lowered apoAII concentrations until they have apparent amyloid deposits, indicating that the presence of amyloid deposits may be responsible for the reduction of apoAII values. In this study, we expanded this concept to other types of systemic amyloidosis. The study attempted to determine whether analysis of apoAII can diagnose amyloidosis in the above underlying diseases or in patients undergoing haemodialysis.

Methods

Serum samples were collected from 21 multiple myeloma (MM) patients, including eight with amyloidosis; 95 rheumatoid arthritis (RA) patients; 73 patients on long term haemodialysis; and 45 control subjects. apoAI and apoAII were measured in 21 multiple myeloma patients, including eight with amyloidosis; 95 rheumatoid arthritis patients, including 45 with amyloidosis; and 73 haemodialysis patients, including 32 with amyloidosis.

Table 1: Apolipoprotein A-I and A-II concentrations in three patient groups that included subjects with amyloidosis and the diagnostic efficiency for amyloidosis in each group

<table>
<thead>
<tr>
<th>Group</th>
<th>Multiple myeloma</th>
<th>Rheumatoid arthritis</th>
<th>Haemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A(−)</td>
<td>A(+)</td>
<td>A(−)</td>
</tr>
<tr>
<td>Number (female)</td>
<td>15 (3)</td>
<td>8 (1)</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>60 (7)</td>
<td>59 (10)</td>
<td>63 (11)</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.3 (0.4)</td>
<td>2.9 (0.6)</td>
<td>3.4 (0.4)</td>
</tr>
<tr>
<td>ApoAI (mg/dl)</td>
<td>114 (35)</td>
<td>111 (39)</td>
<td>116 (26)</td>
</tr>
<tr>
<td>ApoAII (mg/dl)</td>
<td>55 (8)</td>
<td>52 (8)</td>
<td>55 (8)</td>
</tr>
<tr>
<td>Number (female)</td>
<td>13 (5)</td>
<td>8 (1)</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>60 (7)</td>
<td>59 (10)</td>
<td>63 (11)</td>
</tr>
<tr>
<td>Number (male)</td>
<td>42 (17)</td>
<td>34 (12)</td>
<td>40 (17)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>60 (7)</td>
<td>59 (10)</td>
<td>63 (11)</td>
</tr>
<tr>
<td>Serial number</td>
<td>15 (3)</td>
<td>8 (1)</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>60 (7)</td>
<td>59 (10)</td>
<td>63 (11)</td>
</tr>
</tbody>
</table>

Data are shown as mean (SD). A(−): without amyloidosis, A(+): with amyloidosis, NS: not significant, ND: not determined. *Positive by dipstick test, †versus control, ‡versus subjects without amyloidosis in each patient group. §Diagnostic efficiency for amyloidosis in each patient group when the apoAII/AI ratio of 0.2 is adapted as cut off value.
patients, including 45 with amyloidosis; and 73
patients undergoing maintenance haemodialy-
sis (HD), including 32 with amyloidosis. MM
was diagnosed by serum protein analysis and
bone marrow cytology. Diagnosis of RA was
according to the 1987 revised criteria of the
American Rheumatism Association. All the RA
subjects underwent histological examination of
biopsy specimens of kidney (two cases) or
gastroduoedonal mucosa (93 cases), and 50
subjects who were negative for amyloid depos-
ts were defined as RA without amyloidosis.
Eight subjects who were defined as MM with
amyloidosis were positive for amyloid deposits
in rectal mucosa (two cases) or kidney (six
cases). Thirteen MM subjects, though not his-
tologically examined, were suspected not to
have amyloidosis because of absence of symp-
toms that would indicate amyloid involvement,
such as macroglossia, diarrhoea, or carpal tun-
nel syndrome. For HD subjects, amyloid
involvement was suspected by the presence of
carpal tunnel syndrome or cystic changes in
radiography of carpal and shoulder bone,
which strongly suggest the involvement of
amyloid deposits.7 As a control, serum samples
were also collected from 41 healthy adults.
Table 1 summarises the details. None of MM
or RA subjects underwent HD. Subjects with
familial hypercholesteraeia and cholesterol
er est transfer protein deficiency were not
included, as these conditions can affect serum
concentrations of apolipoprotein independently of amyloid involvement.

Apolipoprotein AI (apoAI), an apoprotein
that constitutes high density lipoprotein
(HDL) with apoAII, and apoAII were quanti-
tified in serum by an automated turbidimetric
immunoassay (Eiken Chemical, Tokyo, Japan).
Acute phase serum amyloid A protein (SAA),
which can indicate inflammatory activity, were
measured by a latex agglutination
immunoassay.8 Data were analysed using
Student’s t test.

Results
ApoAI values were reduced in the patient
groups compared with the control group,
although not to a statistically significant
degree, except in the RA group without
amyloidosis. In addition, there was no signifi-
cant difference in these values between those
with and without amyloidosis within each
group (fig 1, table 1). In contrast, apoAII values
were significantly reduced in all patient groups
compared with controls. These values were
reduced in subjects with amyloidosis compared
with those without amyloidosis in each group
and to a statistically significant degree within
the RA group (fig 1, table 1). ApoAII/apoAI
ratio indicated the involvement of amyloidosis
in each group (fig 1, table 1). In the RA group
including both amyloidosis and non-
amyloidosis, no significant relation between
SAA values and the apoAII/apoAI ratio was
found (fig 2). The ratio of 0.2 had diagnostic
sensitivity and specificity for amyloidosis: 50%
and 100%, respectively, in MM; 80% and 78%,
respectively, in RA; and 46% and 90%, respec-
tively, in HD (table 1).
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The apoAII/apoAI ratio was the most effective in RA as a diagnostic marker for amyloidosis. The strict selection of subjects may be responsible for this. Negative results of biopsy do not always rule out the presence of amyloid deposits. A more reliable examination, such as isotope labelled serum amyloid P-component scanning, should be introduced in future studies. The number of MM subjects should be further increased. Poor differentiation of amyloidosis by apoAII/apoAI in HD subjects may be because of the non-biopsy based diagnosis of subjects or may be related to distinct distribution of amyloid deposits, mainly bones and joints, in this type.

In conclusion, the determination of apoAII/apoAI ratio can potentially be a convenient biochemical method to suspect involvement of amyloid deposits in underlying disorders, especially in RA.

Figure 2 Relation between serum amyloid A concentrations (SAA) and the apolipoprotein AII/AI ratio (ApoAII/ApoAI) in 50 rheumatoid arthritis patients with (closed circle, n=25) and without (open circle, n=25) amyloidosis.

Discussion

Taking the findings of this study and the previous report on familial amyloidotic polyneuropathy together, a reduction in apoAII concentrations may be a common phenomenon in systemic amyloidosis. To differentiate amyloid involvement more efficiently, adoption of the apoAII/AI ratio proved successful. This is reasonable, as apoAII concentrations change in good agreement with apoAI, the major protein constituents of HDL. Division of apoAII by apoAI may diminish the effects of quantitative variations in HDL and influential factors common to apoAI and apoAII.

The reason for the reduction in apoAII concentrations in systemic amyloidosis is unknown. Inflammatory conditions may change apolipoprotein composition of HDL, but the apoAII/apoAI ratio was not affected by inflammatory status, which was indicated by SAA values, in the RA subjects (fig 2). Renal dysfunction and malabsorption should also be taken into account. In the RA amyloidosis subjects, the apoAII/apoAI ratio (mean(SD), 0.16 (0.02)) of 12 non-proteinuric RA amyloidosis subjects were not significantly different from those (0.17 (0.05)) of 33 non-proteinuric RA amyloidosis subjects. Serum albumin concentrations of each group show no marked nutritional changes in the amyloidosis group (table 1). Thus, the above conditions may not cause a dominant reduction in apoAII, but may reduce both apoAI and apoAII evenly.

ApoAII forms amyloid fibrils in a type of murine senile amyloidosis, 10 and such mice have low apoAII concentrations. However, apoAII has not been demonstrated in any type of human amyloid deposits. It was shown that the expression of apoAII in the liver was unchanged and secretion of apoAII into urine was increased in familial amyloidotic polyneuropathy, suggesting that HDL from amyloid patients has a lowered affinity for apoAII. 11 12 It should be investigated whether this is the result of the direct interaction of HDL with amyloid deposits (regardless of type) or the result of changes in lipoprotein metabolism in subjects with generalised amyloidosis.

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References

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