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CLINICAL RESEARCH STUDY

Diagnostic Performance of ^{123}I-Labeled Serum Amyloid P Component Scintigraphy in Patients with Amyloidosis

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ABSTRACT

PURPOSE: To assess the diagnostic accuracy and additional information provided by ^{123}I-labeled serum amyloid P component (SAP) scintigraphy in patients with systemic and localized amyloidosis.

SUBJECTS AND METHODS: ^{123}I-labeled human SAP was injected intravenously into 20 controls and 189 consecutive patients with histologically proven amyloidosis: of AA type in 60 cases, AL type in 80, hereditary ATTR type in 27, and localized amyloidosis in 22 cases. SAP scintigrams were obtained 24 hours after tracer injection and were analyzed for abnormal patterns of uptake. Sensitivity and specificity were determined, and scintigraphic findings were compared with clinical data.

RESULTS: Diagnostic sensitivity of SAP scintigraphy for systemic AA, AL, and ATTR amyloidosis was 90%, 90%, and 48% respectively, and specificity was 93%. The distribution of amyloid was less diverse in AA than in AL type. Myocardial uptake was not visualized in any patient. Splenic amyloid was very frequent (80%) in AA and AL type but rarely detected clinically (14%). Abnormal tracer uptake in the liver and kidneys correlated with disturbed liver function and proteinuria, respectively. Bone marrow uptake was specific for AL (21%) and was more frequent in AL kappa than AL lambda. Localized amyloid deposits were not imaged.

CONCLUSION: SAP scintigraphy is diagnostic of amyloid in most patients with AA and AL type but fewer with hereditary ATTR type, relating to differing distributions and burdens of amyloid in these disorders. It usually reveals more widespread organ involvement than is identified clinically, and certain distributions of amyloid are characteristic of particular fibril types.

KEYWORDS: Systemic amyloidosis; Serum amyloid P component; Scintigraphy

Detection of amyloid in a biopsy specimen warrants further clinical evaluation to determine its type, clinical significance, and extent. It is particularly important to make a distinction between systemic and localized forms of amyloidosis, which can be found in the oropharynx, upper airways, ureters, bladder, skin, and eyelids,[1] and have a vastly better prognosis than systemic forms. The 3 major systemic types are amyloid type A (AA), amyloid associated with light chains (AL), and amyloid associated with transthyretin (ATTR) amyloidosis.[2] AA amyloidosis is associated with longstanding inflammatory disorders, and nephropathy is its predominant clinical feature. AL amyloidosis is associated with free light chains producing monoclonal plasma cell dyscrasias and has remarkably diverse clinical manifestations. Hereditary ATTR amyloidosis is associated with mutations of the transthyretin (TTR) gene and presents mainly with neuropathy and cardiomyopathy.[2]

All amyloid deposits contain the nonfibrillar glycopro-

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tein amyloid P component, which is derived from and identical to serum amyloid P component (SAP).[1,3] SAP binds in a calcium-dependent manner to amyloid fibrils of all types.[3] SAP labeled with radioactive ^{123}iodine (^{123}I-SAP) has been used as a tracer to detect amyloid and to determine the extent and distribution of amyloid deposits in systemic AL, AA, and ATTR amyloidosis by scintigraphy and turnover studies.[4-9] The majority of experience with SAP scintigraphy has, however, been accrued in just a single center.

The aim of the present study was to independently reproduce and assess the diagnostic accuracy of and additional information provided by ^{123}I-SAP scintigraphy in our Dutch amyloidosis practice. We report here clinical and scintigraphic findings, and their correlation in 189 consecutive patients with biopsy-proven localized and systemic amyloidosis of AA, AL, and hereditary ATTR types who have been assessed over 10 years.

CLINICAL SIGNIFICANCE

- Serum amyloid P component (SAP) scintigraphy is diagnostic in most patients with AA and AL amyloidosis.
- Abnormal tracer uptake in the liver and kidneys correlate with disturbed liver function and proteinuria respectively.
- SAP scintigraphy usually reveals more widespread organ involvement than is identified clinically.
- Certain SAP scintigraphic patterns are characteristic of particular fibril types.

METHODS

Patients

All 219 consecutive patients with histologically proven amyloidosis who were evaluated at Groningen University Hospital, a tertiary referral center, from February 1990 until December 2003 were prospectively screened for the study. Patients were classified to have systemic amyloidosis of the AA, AL, or hereditary ATTR type, or localized amyloidosis.[10]

Amyloid was diagnosed in all patients by the presence of typical apple-green birefringence in polarized light in a tissue specimen stained with Congo red dye. Localized amyloidosis was defined by its typical clinical presentation of only one tissue affected with amyloid, despite a rigorous search of amyloid in other sites, such as rectum, bone marrow, and subcutaneous fat. Systemic amyloidosis was defined either by the detection of amyloid in a biopsy of kidney, liver, nerve, spleen or subcutaneous fat, or by positive biopsies derived from at least 2 different organs or tissues. AA amyloid was distinguished immunohistochemically using monoclonal murine anti-human AA antibodies (Reu.86.2, Euro-Diagnostica, Arnhem, The Netherlands). AL amyloid was defined by the detection of a clonal plasma cell dyscrasia in patients whose amyloid deposits were negative immunohistochemically for AA type. A clonal plasma cell dyscrasia was diagnosed when a free kappa or lambda light chain was detected in serum or urine by immunofixation electrophoresis or when a relative excess of cells producing 1 of the 2 light chains was detected in bone marrow. In patients with only cardiomyopathy or neuropathy, a mutation in the TTR gene was excluded before the diagnosis of AL amyloid was accepted. ATTR amyloid was defined by the detection of a TTR mutation in patients whose amyloid deposits stained specifically with anti-TTR antibodies (Dako, Copenhagen, Denmark).[10] Twenty control subjects were studied, comprising patients who had diseases that can underlie amyloidosis, but in whom biopsies for amyloid had been negative and no features suggesting amyloidosis had developed during follow-up of 2 to 8 years. The local Ethics Committee approved the study, and all patients and controls who gave informed consent were included. Thirty amyloid patients who did not participate (12 AL, 8 AA, 2 ATTR, 3 localized, and 5 unclassified) were not included for a variety of reasons, including inability to classify their fibril type in 5, logistical problems in 10, individual preference in 6, or through severe illness or death before scintigraphy could be scheduled in 9.

Clinical Evaluation of Organ Involvement

All patients were evaluated in a standardized way, and organ involvement was assessed according to established criteria[11] with some small modifications. The heart was considered to be involved when clinical heart failure (NYHA grade 3 or 4), low voltage electrocardiogram, or mean left ventricular wall thickness $>$ 12 mm was present. Liver involvement was defined as liver span measuring $>$ 16 cm or an elevated serum alkaline phosphatase ($>$180 IU/l, ie, 150% of upper reference limit) was present. Pulmonary amyloid was defined as pulmonary infiltrates on standard chest radiography that were not related to heart failure. Splenic amyloid was defined when it was $>$ 13 cm on ultrasound scanning or when Howell Jolly bodies were present in the blood film. Bone marrow involvement was defined as amyloid present in a bone marrow biopsy, although these were performed systematically only in patients with AL amyloidosis. Renal amyloid was defined as proteinuria ($>$0.5 g per day) or endogenous creatinine clearance (ECC) $<$ 60 mL/min. Clinically overt adrenocortical insufficiency was sought in all patients. Joint involvement was defined by the 'shoulder pad' sign or other unexplained stiffness, deformity, or restriction of hand joints. Carpal tunnel syndrome (CTS) was present when both typical symptoms and a positive Tinel sign were present. In all cases, other causes that might explain the increased size or disturbed function of the organ were excluded.