AA Amyloidosis and AL Amyloidosis

Table 3. New Classification of Amyloidosis. (Primary Amyloidosis Research Committee, Ministry of Health and Welfare, Japan, 1993)

Type of Amyloidosis	Amyloid protein	Precursor protein
I Generalized (systemic) amyloidosis		
1 Immunocytological Amyloidosis		
1) AL amyloidosis	AL	L chain (κ , λ)
2) AH amyloidosis	AH	Ig γ
2: Reactive AA amyloidosis	AA	Apo SAA
3: Familial Amyloidosis		
1) FAP I	ATTR	Transthyretin
2) FAP II	ATTR	Transthyretin
3) FAP III	AApoAI	apo AI
4) FAP IV	AGel	Gelsoline
5) Familial Mediterranean Fever	AA	ApoAA
6) Muckle-Wells' syndrome	AA	ApoAA
4: Dialysis amyloidosis	AB2M	β 2-microglobulin
5: Senile TTR amyloidosis	ATTR	Transthyretin
II Localized amyloidosis		
1: Cerebral amyloidosis		
1) Alzheimer type dementia (Down's syndrome)	A β	β protein precursor
2) Cerebrovascular amyloidosis	A β	β protein precursor
3) Hereditary amyloid cerebral hemorrhage (Dutch)	A β	β protein precursor
4) Hereditary amyloid cerebral hemorrhage (Iceland)	ACys	Cystatin C
5) Creutzfeldt-Jacob disease Gerstmann-Sträussler Scheinker syndrome	AScr	Scrapie protein precursor
2: Endocrine amyloidosis		
1) Medullary carcinoma of the thyroid	ACal	(pro) calcitonin
2) Diabetes type II, Insulinoma	AIAPP	IAPP: Islet amyloid polypeptide (Amylin)
3) Isolated atrial amyloid	AANF	Atrial natriuretic peptide
3: Cutaneous amyloidosis	AD	Keratin
4: Localized tuberosus amyloidosis	AL	L-chain (κ , λ)

2. AA Amyloidosis and AL Amyloidosis

Takashi ISOBE

Key words: SAA (Serum AA), BJP (Bence Jones protein), Sub-subgroup system of BJP

AA protein (Amyloid A) is derived from the amyloid-precursor protein of SAA (Serum AA). SAA is purified from sera with highly positive CRP using column chromatography, while AA is purified from heavily-laden amyloidotic tissue first through repeat homogenation with PBS, then water extractions, followed by chromatography under restricted conditions. Molecular weight of SAA and AA are approximately 13,000 and 9,000 daltons, respectively. Using anti-AA it is possible to demonstrate the localization of AA deposits by immunoperoxidase staining. AA deposits illustrate clinically one type of systemic amyloidosis, ie, secondary or reactive amyloidosis, with characteristic deposit in the spleen, kidney, thyroid, adrenal, pancreas and gastro-intestinal tract. Predisposing clinical entities to AA amyloidosis include rheumatoid arthritis and its related disorders (JRA, Sjögren or Caplan syndrome), Behçet's disease, tuberculosis, syphilis, leprosy, pulmonary empyema, Hodgkin's disease, and some other malignancies. Persistently high titers of SAA monitored by radio-immunoassay using anti-AA in sera from patients with RA or other disorders may well represent one risk factor in the formation of amyloid deposits (1, 5).

AL protein (amyloid of light chain of immunoglobulin) is

derived from precursors of serum-M-protein and/or urinary Bence Jones protein (BJP). AL deposits demonstrate clinically another type of systemic amyloidosis, consisting of both primary amyloidosis and myeloma-associated amyloidosis. Therefore, the predisposing clinical entities are undefined or myeloma-macroglobulinemia. Characteristic deposits of AL are to heart, tongue, skeletal muscles, gastro-intestinal tract, ligaments, and peripheral neurons. Prognosis of AL amyloidosis depends on the localization of organs and severity of deposits. Reported median survival rate of heart amyloid showed only 4 months from the diagnosis, whereas that of peripheral-neuropathy-amyloid showed 50 months, with a median survival of 12 months among total AL amyloidosis. Although complete amino acid sequence studies are time-consuming analyses, they could make a significant contribution to the understanding of AL amyloidosis. It is now well known that there is a predominance of BJP only without serum-M-protein among patients with AL amyloidosis and a high incidence of lambda BJP, compared with a high incidence of serum-M-proteins and a high ratio of kappa BJP among straight myeloma and macroglobulinemia without amyloidosis. Our recent study on various BJP's opened up a new category of sub-subgroup system of BJP, to clarify

amyloidogenicity among BJP's (1-4).

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3. Transthyretin and Familial Amyloidotic Polyneuropathy

Yukio ANDO, Shukuro ARAKI* and Masayuki ANDO

Key words: familial amyloidotic polyneuropathy, transthyretin, amyloid deposition

Introduction

Familial amyloidotic polyneuropathy (FAP) is a heterogeneous collection of familial diseases marked by the systemic accumulation of amyloid fibrils in the peripheral nerves and other organs (1, 2). Our knowledge of the biochemical nature of the amyloid fibril proteins in these hereditary syndromes is limited. Currently, the disease is subclassified according to the following clinical features and ancestry or geographic origin: Type I, polyneuropathy with onset in the lower limbs and severe autonomic dysfunction (Portuguese, Japanese, Swedish, and Jewish families); Type II, polyneuropathy with onset in the upper limbs and mild autonomic dysfunction (Swiss-German families); Type III, polyneuropathy, renal failure, and peptic ulcer; and Type IV, progressive cranial neuropathy, and lattice corneal dystrophy (Finnish, Irish, American and Japanese families) (3, 4).

Recent studies have revealed that replacement of valine-30 of transthyretin (TTR) by methionine is a prerequisite to the formation of amyloid deposit in FAP Type I (1, 2). Furthermore, owing to the progress of molecular genetics, various other types of FAP with different positions of amino acid substitution in TTR have been reported (5-7).

Clinical features and genetics of FAP

The inheritance pattern is autosomal dominant with a high penetrance rate and an equal sex ratio. The symptoms are first recognized when the patient is between 18-69 yrs of age, with a mean age of onset of 34.8 yrs. Evidence of a sensory dominant mixed type peripheral neuropathy is usually manifested in the lower limbs: dissociation of sensory impairment is common, with pain and temperature sensation being the most severely

affected. Autonomic nervous system involvement, such as dyshidrosis, sexual impotence, alternating diarrhea and constipation, orthostatic hypotension, and urinary incontinence are frequent (Fig. 1). A recent study of peripheral autonomic dysfunction by laser Doppler flowmetry revealed that autonomic nerves are first impaired in FAP patients (8).

Detection of variant TTR and mutations in TTR

Biochemical studies revealed that amyloid fibril protein of type I FAP consists of a TTR variant caused by a single amino acid substitution, methionine for valine at position 30. Recently, FAP and its carrier state were identified by the detection of a TTR variant in the serum. To detect the extra methionine at position 30, cyanogen bromide cleavage was carried out, and anomalous peptide fragments from variant TTR were quantitatively detected by a RIA system.

To determine a DNA diagnosis of FAP, we cloned TTR cDNAs from a human liver cDNA library. The TTR variant has the single amino acid substitution: Val 30, which is coded by GTG, is substituted by Met, which should be coded by ATG. The transition from G to A in this region of the TTR gene creates both Nsi I (5'-ATGCAT-3') and a Bal I (5'-TGGCCA-3') restriction sites. Accordingly, a carrier of this type of mutation should be detectable by digesting genomic DNAs with either Nsi I or Bal I, followed by Southern blot hybridization, using the TTR cDNA as a probe. These analyses revealed that most of FAP patients are heterozygous for the TTR gene and carry one normal and one mutant gene (9).

Transgenic mice of FAP

Recently Wakasugi et al have produced transgenic mice by microinjecting the cloned human mutant TTR gene into ferti-

The First Department of Internal Medicine, Kumamoto University School of Medicine, and *Emeritus Professor of Kumamoto University, 1-1-1 Honjo, Kumamoto 860