Is familial amyloid polyneuropathy rare?

DNA testing is changing the concept of this disease

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Familial amyloid polyneuropathy (FAP) is one type of hereditary generalized amyloidosis, initially showing polyneuropathy and autonomic dysfunction but with later involvement of many visceral organs. The disease is caused by a mutation in the transthyretin (TTR) gene, which produces an amyloidogenic variant form of TTR (ATTR), thus leading to the designation ATTR type FAP.[1] Up to now, more than 100 mutations have been identified as a cause of the gene abnormality in this disease,[2] but the substitution of methionine for valine at position 30 (ATTRVal30Met) is the most common one that causes the classic phenotype of FAP. With regard to the clinical concept of ATTR type FAP, the following features have been emphasized.[3] The disease occurs mainly in four endemic areas (the Oporto area in Portugal, Skellefteå in Sweden, and Arao and Ogawa in Japan) where it is inherited as an autosomal dominant trait with equal sex distribution. The age at onset is the late 20s to early 40s and polyneuropathy is consistently associated with sensory dissociation; that is, pain and thermal sensations are predominantly affected at an early stage of the disease. Various autonomic dysfunctions, including severe orthostatic hypotension, urinary incontinence, and disturbed bowel movement with alternating constipation and diarrhea, invariably appear.

However, since the gene diagnostic technique became available, the number of patients with ATTR type FAP has been increasing, and it is clear that the clinical characteristics mentioned above are not consistent with the vast majority of recently identified cases: they had no genealogical relationship with endemic foci of this disease, and clinical phenotypes vary according to diverse TTR gene mutations. Even in the FAP patients with ATTRVal30Met, the clinical manifestations in patients originating from nonendemic areas are considerably different from those in patients from endemic foci[4]: the former first show symptoms in their 60s and a negative family history at referral is common among them. Males are predominantly affected and many patients show chronic progressive sensorimotor neuropathy in which dissociated sensory loss or autonomic failure is not always prominent.

Since ATTR type FAP kindreds have now been shown to exist in many nations worldwide,[5] FAP seems not to be so rare a disease as previously thought. However, the classic concept of the disease is strong in the minds of many neurologists, so that patients with nonfamilial ATTR type FAP are often late to receive a correct diagnosis. In this issue of *Neurology*, Plante-Bordeneuve et al.[6] deal with the diagnostic pitfalls in the examination of patients with nonfamilial (sporadic) ATTR type FAP. They reviewed the clinical data of 90 patients with ATTR type FAP proven by DNA testing. They consisted of 21 women and 69 men with a mean age at onset of 61 years and of 17 different mutations of the TTR gene including 38 cases with Val30Met, 16 with Ser77Tyr, 15 with Ile107Val, and 5 with Ser77Phe. The mean interval to diagnosis was 4 years, ranging from 1 to 10. All sensations were affected in 60 patients (67%), while small fiber dysfunction predominated in others. Eighty patients (90%) had severe dysautonomia and 12 were treated by implantation of a pacemaker. Eighteen patients were mistaken for chronic inflammatory demyelinating polyneuropathy (CIDP), which was the most common diagnostic error; these patients had been managed with high doses of IV immunoglobulin and corticosteroids for several years. An initial symptom of paresthesia in the distal lower limbs, decreased nerve conduction velocity, increased CSF protein, and negative biopsy findings for amyloid deposits were shown to be main causes of diagnostic error. If enough attention had been paid to the presence of autonomic and/or cardiac dysfunction,[7] neither of which appear in CIDP, the possibility of amyloid neuropathy might have been considered in the differential diagnosis. It is also important to keep in mind that biopsy findings can be mislead-

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ing: due to the random distribution of amyloid deposits the absence of amyloid deposition in one biopsy specimen cannot rule out the diagnosis of amyloidosis. In such situations it is recommended to examine serial sections of the whole specimen or to send the specimens to a pathologist familiar with amyloidology. The authors conclude that DNA testing should be performed in patients with progressive polyneuropathy of unknown cause to avoid misdiagnosis of ATTR type FAP.

A delay in correct diagnosis may reduce the chance of adequate treatment for patients: since ATTR is produced mainly in the liver, liver transplantation has been widely employed as the only curative therapy for patients with ATTR type FAP.[8] However, many of the sporadic patients with ATTR type FAP are not suitable for this current treatment because they are too old to undergo this challenging operation or frequently have severe cardiac amyloidosis. Alternatively, some nonsteroidal anti-inflammatory drugs (NSAIDs) have been proposed as potential candidates for stopping or slowing the deposition of ATTR-derived amyloid. Although the molecular basis of ATTR-related amyloid deposition has not yet been elucidated, dissociation of a TTR tetramer and subsequent misfolding of a TTR monomer are the critical processes for amyloid fibril formation in the disease and it has been demonstrated that in comparison to the wild type of TTR, ATTR tetramers are less stable and more easily dissociated, finally forming into amyloid fibrils.[9] It has recently been shown that some NSAIDs are able to bind tightly to TTR molecules and to increase this stability,[10] which is expected to suppress ATTR-derived amyloidogenesis. If drug therapy becomes applicable to ATTR type FAP, many patients who cannot undergo liver transplantation or asymptomatic gene carriers will be able to receive noninvasive treatment. To provide such therapeutic options for patients, early and accurate diagnosis of ATTR type FAP is necessary.

REFERENCES

1. Westermark P, Benson MD, Buxbaum JN, et al. Amyloid: toward terminology clarification. Report from the nomenclature committee of the international society of amyloidosis. Amyloid 2005;12:1–4.
2. Connors LH, Lim A, Prokaeva T, Roskens VA, Castello CE. Tabulations of human transthyretin (TTR) variants, 2003. Amyloid 2003;10:160–184.
3. Andrade C. A peculiar form of peripheral neuropathy. Familiar atypical generalized amyloidosis with special involvement of the peripheral nerves. Brain 1952;75:408–427.
4. Misu K, Hattori N, Nagamatsu M, et al. Late-onset familial amyloid polyneuropathy type I (transthyretin Met30-associated familial amyloid polyneuropathy) unrelated to endemic focus in Japan. Clinicopathological and genetic features. Brain 1999;122:1951–1962.
5. Reilly MM, Adams D, Booth R, et al. Transthyretin gene analysis in European patients with suspected familial amyloid polyneuropathy. Brain 1995;118:849–856.
6. Plante-Bordeneuve V, Ferreira A, Lalu T, et al. Diagnostic pitfalls in sporadic transthyretin familial amyloid polyneuropathy (TTR-FAP). Neurology;69:693–698.
7. Rapezzi C, Perugini E, Salvi F, et al. Phenotypic and genotypic heterogeneity in transthyretin-related cardiac amyloidosis: towards tailoring of therapeutic strategies. Amyloid 2006;13:143–153.
8. Stangou AJ, Hawkins PN. Liver transplantation in transthyretin-related familial amyloid polyneuropathy. Curr Opin Neurol 2004;17:615–620.
9. Sekijima Y, Wiseman RL, Matteson J, et al. The biological and chemical basis for tissue-selective amyloid disease. Cell 2005;121:1–13.
10. Tojo K, Sekijima Y, Kelly JW, Ikeda S. Diflunisal stabilizes familial amyloid polyneuropathy-associated transthyretin variant tetramers in serum against dissociation required for amyloidogenesis. Neurosci Res 2006;56:441–449.