FAP is a Candidate Disease in Patients with Undetermined Polyneuropathy

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Transthyretin (TTR)-related familial amyloidotic polyneuropathy (FAP) is a fatal hereditary amyloidosis whose amyloidogenic precursor protein is amyloidogenic TTR (ATTR) (1, 2). Patients with FAP show various serious symptoms, such as cardiac and renal dysfunction, gastrointestinal and ocular disorders, glandular and autonomic dysfunction, in addition to peripheral polyneuropathy. Until 25 years ago, FAP was thought to be a disease restricted to endemic occurrence in only certain areas. However, owing to progress in biochemical and molecular genetic analyses, this disease is now believed to occur worldwide (2). To date, reports of more than 100 different points of single or double mutations, or a deletion in the TTR gene, have been published, and several different phenotypes of FAP, such as neuropathic, cardiac oculoleptomeningeal types, have been documented.

In Japan as well, FAP was once considered to be restricted in the endemic areas, such as Kumamoto and Nagano districts in Japan, and identified amyloidogenic TTR (ATTR) was only ATTR V30M. Kato-Motozaki et al recently performed an epidemiological study of FAP, and found the prevalence of the disease was 0.87-1.01 per 1,000,000 persons in Japan (3). However, at present, 26 different points of mutation have been identified, and many sporadic late onset FAP patients have been identified throughout Japan. Proteomics analysis for variant TTR in serum in addition to genetic testing led to the change in the known prevalence and concept of FAP, as Ikeda previously emphasized (4).

Shirota et al presented a 57-year-old Japanese FAP patient with predominant upper-limb involvement, the pattern of which resembled a mononeuropathy multiplex pattern (5). Pathological examinations for sural nerve biopsy failed to diagnose the disorder, but that for lung partial resection performed later for other diagnostic purposes suggested FAP. A rare mutation in the transthyretin gene (S50R) was subsequently confirmed by means of genetic testing. In their report, the patient had no autonomic dysfunction or any family history for FAP.

Misu et al previously reported the clinicopathological and genetic features assessed in 35 Japanese families affected by late-onset FAP ATTR V30M whose siblings were unrelated to Kumamoto and Nagano (6). The age of those patients was over 50, and the most common initial symptom was paraesthesia in the legs. Autonomic symptoms were generally mild and did not seriously affect daily activities. Interestingly, the male-to-female ratio was extremely high (10.7 to 1). Moreover, a family history was evident in only 11 out of 35 families, and the other patients were apparently sporadic. Some of the patients had been misdiagnosed as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). As in the case presented by Shirota et al (5), FAP is sometimes difficult to diagnose or it is misdiagnosed as another neuropathic disorder.

Concerning FAP ATTR S50R, 11 cases have been reported worldwide, and all of those patients seem to have typical initial symptoms of FAP. However, the symptoms of the case presented by Shirota et al (5) first showed upper limb manifestations which were not suspicious of FAP. It has been widely accepted that polyneuropathy usually starts at the distal portion of the lower limb. However, in FAP, various non-neuropathic symptoms can become an initial symptom of FAP. In addition, clinical manifestations in the upper limb sometimes become an initial symptom of FAP.

It has been widely accepted that liver transplantation can halt the progression of FAP. In addition, several therapeutic trials with drugs for FAP are now on going, FAP is now becoming a treatable disease. As demonstrated in the report by Kato-Motozaki et al (3), FAP patients and medical doctors living in the endemic areas have an increased awareness of the clinical symptoms and treatment for FAP. In contrast, those living in non-endemic areas sometimes are not aware...
of the disease. Therefore, if we encounter patients with unknown neuropathy, even if the patient complains of upper limb signs, it is important to suspect FAP and perform a biopsy of gastrointestinal tract, sural nerves, or abdominal fat tissues to confirm the presence or absence of amyloid deposition. If amyloid deposition is confirmed, immunohistochemical staining using anti-human TTR antibody should be performed to determine the type of amyloidosis.

Recently, attention has been paid to senile systemic amyloidosis (SSA). The amyloid deposition in the tissues in this type of amyloidosis, is formed by wild type TTR. Therefore, to distinguish FAP from SSA, we must examine the presence or absence of a mutation in TTR gene or variant TTR by means of mass spectrometry or genetic testing. An accurate diagnosis can save the FAP patient’s life.

References