Cautions after Liver Transplantation for Familial Amyloidotic Polyneuropathy

Key words: cerebral embolism, cardiomyopathy

Polyneuropathy or peripheral neuropathy is a set of clinical syndromes of muscle weakness, sensory disturbance, and impairment of deep reflexes caused by diffuse lesions of peripheral nerves. It is classified into acute or chronic types based on the clinical course, and is also classified into hereditary or acquired types based on the etiology. Hereditary polyneuropathies are consisted of Charcot-Marie-Tooth syndrome (peroneal muscular atrophy), Dejerine-Sottas disease, Refsum disease, hereditary sensory neuropathy, hereditary predisposition to pressure palsies, Fabry disease, and abetalipoproteinemia etc. On the other hand, acquired polyneuropathies are consisted of Guillain-Barre syndrome, Miller-Fisher syndrome, chronic demyelinating polyneuritis, acute and chronic idiopathic sensory neuropathy, acute pandysautonomia, plexus neuropathy, vasculitic neuropathy, and neuropathies associated with metabolic disorders such as diabetes mellitus, hypothyroid, acromegaly, uremia, and so on.

Amyloidotic polyneuropathy (AP) is classified in both hereditary and acquired classes. Acquired AP develops symptoms in kidney, heart, tongue, liver, spleen, and also develops carpal tunnel syndrome and malabsorption, but rarely involves nervous system (only 14%). In contrast, hereditary AP (also called familial AP, FAP) frequently involves peripheral nerves (93%). Amyloid is an insoluble extracellular aggregate of protein sheets, and forms in nerves and other tissues when any of many proteins is excessively produced. Clinical presentations of AP include gradually progressive autonomic neuropathy, symmetric loss of pain and temperature sensation with spared position and vibratory senses. The diagnosis of AP can be established by histologic demonstration of amyloid in nerve or by detection of a transthyretin (TTR) mutation by immunohistochemistry or DNA analysis. FAP is autosomal dominant disorder, and more than 80 different variants have been identified. Among them, FAP is usually classified into 3 main subtypes, type 1 (Andrade type), 2 (Rukavina type), and 3 (Van Allen type), and clinical features of each are different depending on the different genetic mutation of the TTR gene. There is two hot spots of FAP in Japan, in Nagano and Kumamoto prefecture. The Japanese FAP belong to type 1 associated with a substitution of Val 30 to Met.

Therapeutic approaches for FAP include plasmapheresis, immunoadsorption, and orthotopic liver transplantation (OLT) (1). However, OLT is the only way to permanently stop the production of variant TTR. After first OLT was performed in 1990, more than 300 patients have been transplanted throughout the world, and the 5-year survival rate is now approximately 75% following OLT (1). Domino liver transplantation (DLT) have recently been performed in several institutions, in this procedure, the resected FAP livers were then transplanted into non-FAP patients who need transplantation due to diseases such as unresectable primary or metastatic liver cancers, or biliary atresia (2, 3). DLT may be advantageous for expansion of the donor pool, ability to use living donors, and presence of very short ischemic time and thus excellent liver function even though recipients of such grafts must be carefully observed for a possible subsequent cardiomyopathy (4).

OLT is effective to improve sensory and autonomic disturbances after initial 12 months, although motor function and visceral organ damage are not improved (5). Some of the cases showed adverse outcomes including death in cases with duration of illness more than 6 years (1, 6). It is important to note that cardiac amyloidosis can be exacerbated, although plasma TTR levels were decreased substantially and amyloid deposition in FAP is generally inhibited after OLT (7-9). This is probably due to enhanced deposition of wild-type TTR on a template of amyloid derived from variant TTR. The phenomenon may be mutation-dependent, i.e., Pro52 and Thr84 mutations but not Val30 mutation (7, 9). Although neurological and nutritional symptoms improved in the majority of affected patients, echocardiography showed that thickening of ventricular wall and valve progressed postoperatively (7). Furthermore, amyloid deposits involve in the conduction system of the heart that may cause harmful arrhythmic complications. Thus care should be paid to wall thickness and arrhythmia of the heart even after the successful OLT, where an inappropriate movement of the wall may form thrombus at the endocardium, which then causes recurrent cerebral embolism as is reported in this issue of the Journal (10).

Because patients with preexisting cardiovascular abnormalities progress despite transplantation, consideration for combined heart-liver transplantation may be warranted in this subset of patients (8).

See also p 259.
References


