

Familial Amyloid Polyneuropathy: Hypertrophy of Ligaments Supporting the Spinal Cord

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Summary: We describe characteristic spinal MR findings of two cases of familial amyloid polyneuropathy (FAP). Both cases showed leptomeningeal enhancement on contrast-enhanced T1-weighted image. In addition, three-dimensional constructive interference in steady-state imaging demonstrated thickening of the ligaments, other connective tissues within the spinal canal, dura matter, and dorsal nerve roots. These findings in FAP are felt to represent amyloid deposition.

Familial amyloid polyneuropathy (FAP) is one of the groups of hereditary systemic amyloidosis characterized by progressive peripheral polyneuropathy. The precursor proteins of FAP are mutant transthyretin, apolipoprotein AI, or gelsolin. More than 60 single or double amino acid substitutions of transthyretin have been identified, and these groups are called transthyretin-related FAP. In patients with transthyretin-related FAP, many organs such as eye, kidney, and heart can be affected, and autonomic dysfunction occurs (1, 2). Amyloidogenic transthyretin, the pathogenic protein of FAP, is predominantly synthesized by the liver; therefore, liver transplantation for FAP is now considered a promising therapy for saving patients' lives (3).

Although clinical, laboratory, and pathologic investigations for FAP have been performed, radiologic studies are few in number (4, 5). We describe spinal MR findings, in particular high-spatial-resolution imaging findings, of two cases with transthyretin-related FAP.

Case Reports

Case 1

A 51-year-old woman underwent resection of the vitreous of each eye because of vitreous opacity, which caused gradual worsening of visual acuity. Six years after vitreous resection, lower limb dysesthesia appeared along with autonomic symp-

toms, including abdominal discomfort and neurogenic bladder. A biopsy specimen from the sigmoid colon showed amyloidosis (non-AA type). Her older sister had FAP, and her daughters were carriers of FAP. Therefore, her family history, typical visual, and autonomic nervous symptoms suggested FAP. In June 1999, she was admitted to our hospital, and genetic analysis revealed FAP, single amino acid substitution of cysteine for tyrosine at position 114. After the diagnosis of FAP, she received a liver transplant from a living donor.

One year after liver transplantation, transient episodes of righted-sided numbness and dysesthesia began in her right hand and eventually, over 10 minutes, extended over her right thigh and lower limbs. She was again admitted to our hospital to evaluate the neurologic abnormalities associated FAP and underwent MR examination.

The MR examination was performed with a 1.5-T superconductive unit. T1-weighted spin-echo (400/12/2 [TR/TE/NEX]) images of the cervical spinal cord showed slightly but diffuse hyperintensity of surface of the spinal cord, suggesting leptomeningeal involvement (Fig 1A). The dentate ligaments and other ligaments supporting the spinal cord were thick and slightly hyperintense on axial T1-weighted images (500/15/1) (Fig 1B). On T2-weighted fast spin-echo images (3700/112/1), the surface of the spinal cord, which was the area of hyperintensity on T1-weighted images, was slightly hypointense. Contrast-enhanced MR images obtained after intravenous injection of gadopentetate dimeglumine (0.1 mmol/kg) showed diffuse leptomeningeal enhancement, predominantly in cervical and upper thoracic level (Fig 1C).

For the evaluation of three-dimensional constructive interference in steady-state (3D-CISS) images (12/5.9/1; flip angle, 70°), six healthy volunteers (four men, two women; age range, 22–36 years; mean age, 30.0 years) underwent MR imaging at the level of cervical and thoracic spinal cord. The presence or absence of abnormal findings in the patients with FAP was assessed on 3D-CISS images and findings were compared with those of healthy volunteers. Axial 3D-CISS images of case 1 showed thickened dentate ligaments and the cervical septum (Fig 1D). Diffusely thickened dentate ligaments were also well demonstrated as longitudinal low signal intensity band parallel to spinal cord on sagittal 3D-CISS images (Fig 1E). On coronal images, thickened dura matter and tortuous structures dorsal to nerve roots were observed (Fig 1F).

Case 2

A 39-year-old man had a 20-year history of gradual worsening of left visual acuity. At the age of 30, his left visual field constricted and he developed difficulties with light perception. Six years later, the right visual acuity worsened and autonomic nervous dysfunction, including diarrhea and impotence, appeared. His younger brother, four cousins, and seven uncles had familial amyloidosis. His family history and typical visual and autonomic nervous symptoms suggested FAP. He was admitted to our hospital, where genetic analysis revealed FAP, single amino acid substitution of cysteine for tyrosine at position 114. After diagnosis of FAP, he received liver transplantation from a living donor in September 2001. Three months

Received October 29, 2003; accepted after revision January 7, 2004.

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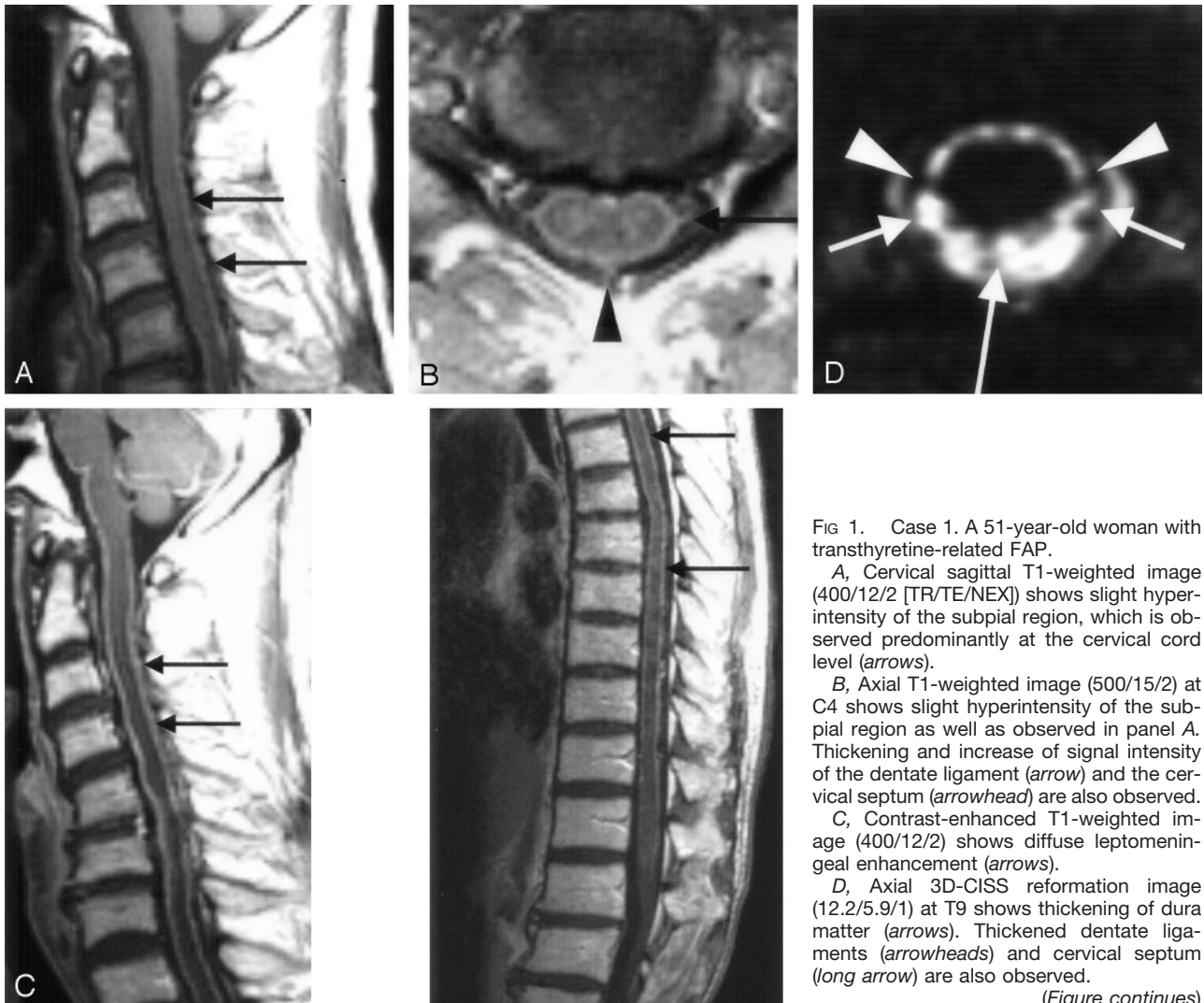


FIG 1. Case 1. A 51-year-old woman with transthyretine-related FAP.

A, Cervical sagittal T1-weighted image (400/12/2 [TR/TE/NEX]) shows slight hyperintensity of the subpial region, which is observed predominantly at the cervical cord level (arrows).

B, Axial T1-weighted image (500/15/2) at C4 shows slight hyperintensity of the subpial region as well as observed in panel A. Thickening and increase of signal intensity of the dentate ligament (arrow) and the cervical septum (arrowhead) are also observed.

C, Contrast-enhanced T1-weighted image (400/12/2) shows diffuse leptomeningeal enhancement (arrows).

D, Axial 3D-CISS reformation image (12.2/5.9/1) at T9 shows thickening of dura mater (arrows). Thickened dentate ligaments (arrowheads) and cervical septum (long arrow) are also observed.

(Figure continues)

after liver transplantation, he underwent MR examination to evaluate CNS abnormalities associated with FAP. At the time of MR examination, physical examination findings were decrease of deep tendon reflex of lower limbs, mild hypesthesia, and hypalgesia of bilateral thigh and lower limbs.

Contrast-enhanced MR images showed diffuse leptomeningeal enhancement, predominantly in cervical and upper thoracic levels (Fig 2A). 3D-CISS images showed thickened dentate ligaments (Fig 2B and C) and cervical septum (Fig 2C).

Although dorsal nerve roots are slightly thicker than ventral nerve roots even in healthy volunteers, dorsal nerve roots of patients were significantly thicker (Fig 2D) than the ventral roots and dorsal roots of healthy volunteers. At the level of thoracic spinal cord, thickened dentate ligaments and arachnoid surrounding spinal cord were observed as low-signal-intensity bundles around the spinal cord (Fig 2E).

Discussion

Leptomeningeal vessels are the principal site of amyloid deposition, as shown in two pathologic studies of 18 patients with systemic amyloidosis, 12 of whom had FAP (6, 7). In these studies, amyloid deposits were found in the leptomeningeal vessels and the pia-arachnoid membranes, predominantly involv-

ing the arteries and arterioles of the subarachnoid cerebral space. Other pathologic studies reported that the mutant transthyretin deposited as extracellular twisted-pleated sheet fibrils in peripheral somatic and autonomic nerves. Unmyelinated and small myelinated fibers are more vulnerable than are large myelinated fibers. Therefore, autonomic dysfunction is often observed before sensorimotor nerve dysfunction manifests, and sensory nerves are more susceptible to impairment than are motor nerves (8). Autopsy studies of FAP have revealed heavy infiltration of amyloid in autonomic ganglions and posterior root of the spine (9, 10).

Although there have been prior pathologic studies in patients with FAP, radiologic imaging reports of FAP are limited. Horowitz et al (4) described one case of FAP with leptomeningeal enhancement on MR images, which indicated amyloid deposition. They speculated that contrast enhancement of leptomeningeal pial and arachnoid amyloid might include an inflammatory reaction to the amyloid deposits with extracellular enhancement outside the blood-cord barrier, lack of wash-out of contrast material due to

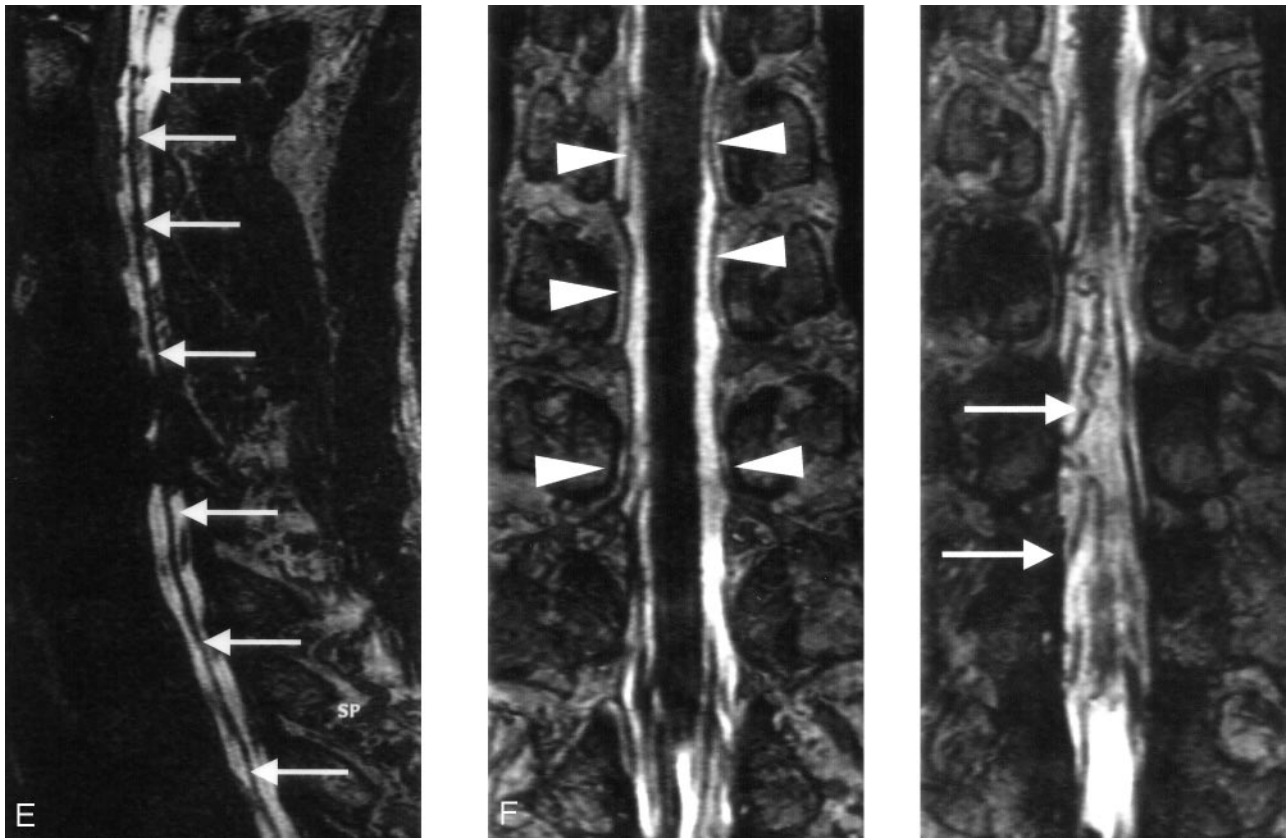


FIG 1. (Continued)

E, Cervical sagittal 3D-CISS image (12.2/5.9/1) shows longitudinal low signal intensity band parallel to the spinal cord (arrows), which represents thickened dentate ligament.

F, Coronal 3D-CISS image (12.2/5.9/1) shows thickened dura matter (arrowheads), and tortuous veins dorsal to spinal cord are well observed (arrows).

altered vascularity or vascular stasis within the abnormal leptomeningeal vessels or tissues, or enhancement of edematous tissue. Our cases showed diffuse leptomeningeal enhancement similar to that in previous reports (4, 5). MR findings of CNS amyloidosis or amyloidoma are heterogeneous on T2-weighted images and isointense to slightly hyperintense on T1-weighted images. The heterogeneous signal intensity is thought to represent nonuniform deposits of amyloid protein. The areas of denser deposition of amyloid are more likely to have higher signal intensity on T1-weighted images.

The marked enhancement following contrast material administration is typical, and this phenomenon may be caused by secondary destruction of the blood-brain barrier attributable to the amyloid involvement in the blood vessel walls that can be seen microscopically (11).

In case 1, pial surface and the dentate ligaments showed slight hyperintensity on noncontrast T1-weighted images. It suggested that dense amyloid deposition occurred in these regions.

Pia mater covers the spinal cord and attaches to the dura mater on the lateral side of the spinal cord. This pial bundle connects between the spinal cord and dura mater, the dentate ligament, and it plays an

important role in supporting the spinal cord. Another arachnoid membrane connecting between pia and dura mater, which become thick at the dorsal cervical spinal cord, is known as cervical septum. We speculate that amyloid deposits on such ligaments and connective tissues consist of pia-arachnoid membrane.

3D-CISS provides high spatial resolution, less CSF artifact than spin-echo T2-weighted imaging, and high contrast-to-noise ratio (12). Marked contrast between CSF and solid structures and high spatial resolution makes possible identification of ultrastructures within the spinal canal. In our cases, only the 3D-CISS image can delineate thickening of the ligaments, connective tissue, dura mater, nerve roots, and vessels. To distinguish among tortuous veins, redundant nerve roots, and thickened arachnoid, we observed the contiguous original, as well as reconstructed CISS, images carefully. The veins could be followed as continuous, curvilinear structures on the CISS images. Dilatation of the outer margin of the veins indicated amyloid deposition to connective tissues surrounding vessels. Thickening of the dorsal nerve root, which indicated it had heavier amyloid deposition than did the anterior root, was consistent with previous autopsy findings (10).

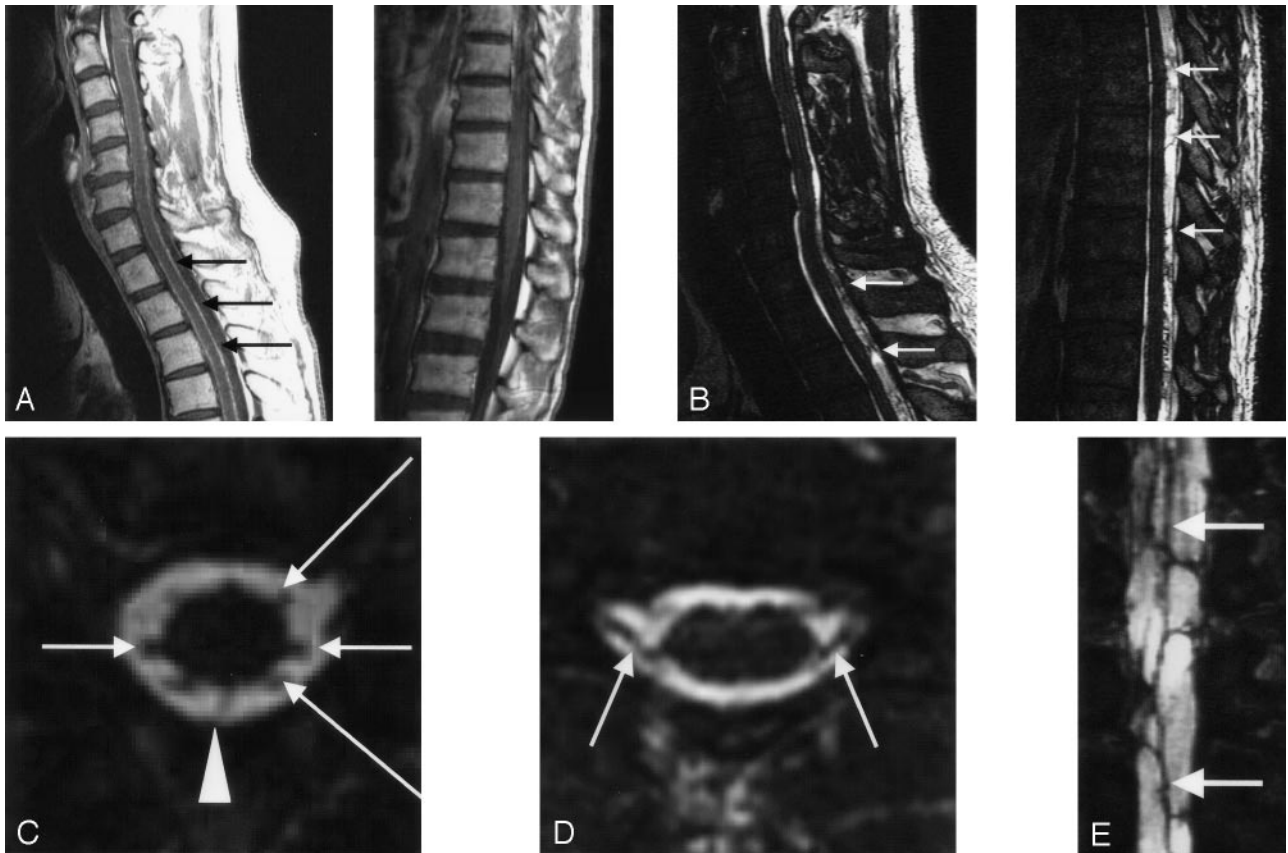


FIG 2. Case 2. A 39-year-old man with transthyretine-related FAP.

A, Contrast-enhanced T1-weighted image (400/12/2) shows diffuse leptomeningeal enhancement predominantly in the cervical and upper thoracic region (arrows).

B, Sagittal 3D-CISS image (12.2/5.9/1) shows low-signal-intensity tiny strands dorsal to the spinal cord (arrows), which represent thickened arachnoid tissue. A thickened dentate ligament was also seen on cervical parasagittal 3D-CISS image (not shown).

C, Axial 3D-CISS reformation image (12.2/5.9/1) at C7 shows thickening of dentate ligaments (arrows) and cervical septum (arrowhead). Long arrows indicate ventral and dorsal nerve roots.

D, Axial 3D-CISS reformation image (12.2/5.9/1) at C3 shows thickening of dorsal nerve roots (arrows).

E, Coronal 3D-CISS reformation image (12.2/5.9/1) of dorsal region of lower spinal cord shows low signal intensity tiny strands (arrows), which represent thickened arachnoid tissue.

Conclusion

Differential diagnosis of diffuse leptomeningeal enhancement includes leptomeningeal dissemination due to malignant diseases, lymphoma, infectious meningitis, and granulomatous diseases. When diffuse leptomeningeal enhancement accompanying hypertrophy of ligaments within the spinal canal is observed, one should consider amyloidosis rather than other above-described diseases. Although neither of our patients underwent surgery or biopsy of spinal lesions, we believe that diffuse leptomeningeal enhancement and hypertrophy of ligaments within the spinal canal suggest amyloid deposition associated with FAP.

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