

Familial Oculoleptomeningeal Amyloidosis

Report of a New Family With Unusual Features

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● A family had a dominantly inherited amyloid angiopathy that involved the meninges of the brain and spinal cord, retina, vitreous humor, peripheral nerves, and systemic organs. Clinical features included hemiplegic migraine, periodic obtundation, psychosis, seizures, intracerebral hemorrhage, myelopathy, visual impairment, deafness, and peripheral neuropathy. Pathological findings consisted of amyloid deposition in the leptomeningeal and retinal vessels, in the vitreous humor, and in perivascular tissue throughout the body. Evaluation of the amyloid showed it to be a transthyretin (prealbumin). A brief course of plasmapheresis produced a short-lived decreased concentration in circulating transthyretin.

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A number of familial forms of amyloidosis that involve the nervous system have been described.¹⁻⁶ We describe an Italian family with an unusual form of amyloidosis that was manifested by hemiplegic migraine, periodic obtundation, psychiatric symptoms, seizures, intracerebral hemorrhage, visual impairment, deafness, myelopathy, and polyneuropathy.

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REPORT OF CASES

CASE 1.—This patient was the twin brother of patient 2 and the uncle of patient 3. At the age of 28 years, he complained of recurring headaches associated with nausea and vomiting. At the age of 31 years, he had difficulty with walking and urinary frequency. Two years later, he was deaf in the left ear, blind in the left eye, and numb on the right side of his body. At the age of 37 years, his mental capacity had deteriorated. He also had a cataract in his left eye and a right-sided Horner's syndrome; his speech was dysarthric; and he had a spastic paraparesis and ataxia, and was wheelchair bound. At this time, a myelogram showed irregular moth-eaten and serpentine filling defects from T-6-T-12. One year later, he had developed a spastic quadriplegia. At the age of 40 years, he was confused and had dysphagia and dysarthria. He also exhibited bilateral cataracts, bilateral nerve deafness, atrophy and fasciculation of the tongue, weakness and wasting of the intrinsic muscles of the hand, and paraspinal atrophy. He was admitted to the hospital and died three weeks later of respiratory failure.

A general autopsy showed pulmonary hemorrhages, chronic pyelonephritis, and cardiac hypertrophy and dilatation. Gross examination of the nervous system revealed a diffusely atrophied brain (1170 g) and a large, flattened membrane that corresponded to an organized hematoma in the left occipital region. The entire pia-arachnoid that covered the cerebral hemispheres, cerebellum, and spinal cord, showed angiomatous thickening. Histologically, these formations disclosed amyloid angiopathy and scanty lymphocytosis. The spinal cord itself was diffusely atrophic with gliosis (Fig 1). The cerebral and cerebellar cortex showed patchy superficial foci of atrophy (Fig 2).

CASE 2.—This patient was the twin sister of patient 1 and mother of patient 3; she

developed headaches associated with nausea, vomiting, and paresthesias in her teens. At the age of 31 years, she saw a physician because of numbness in both legs and urinary frequency. Five years later, she had progressive weakness and hyperreflexia that affected her legs more than her arms. Two myelograms and an electroencephalogram (EEG) at that time were normal. At the age of 37 years, she had horizontal and vertical nystagmus, a left-sided Horner's syndrome, extensor plantar responses, and facial weakness. Soon afterward, she complained of urinary incontinence. At the age of 47 years, she underwent bilateral carpal tunnel surgery. A year later, she awoke one morning and found that she was incontinent of urine and unable to move her legs. There was total paralysis of the left leg and severe weakness in the right leg. This weakness gradually improved. At the age of 49 years, her hands were stiff, and she experienced pain and numbness in them. She also noted that she would burn her hands and forearms without feeling any pain. During the next two years, she noticed difficulty in finding words and a deterioration in her memory.

At the age of 51 years, she was admitted to our institution for evaluation. She was alert and able to manage for herself, but walked with a crutch. Her speech was mildly dysarthric, and she made paraphasic errors. There was wasting and weakness of the thenar muscles bilaterally. While the right leg had normal strength, the left leg was spastic and weak. Deep tendon reflexes were diffusely hyperactive. There were bilateral extensor plantar responses. Sensation to pinprick was impaired over both hands, as well as the right leg and trunk up to the lower thoracic region. Joint position sensation was impaired in the left toes. While sharp/dull and hot/cold discrimination were present in the hands, the patient could readily immerse her fingers

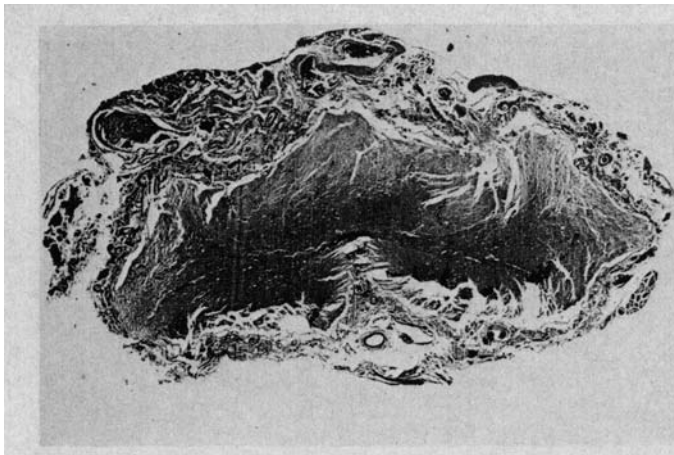


Fig 1.—Case 1. Lower thoracic spinal cord at level of maximum compression showing severe atrophy and gliosis. Note marked meningeal thickening with amyloid deposits (hematoxylin-eosin, original magnification $\times 30$).

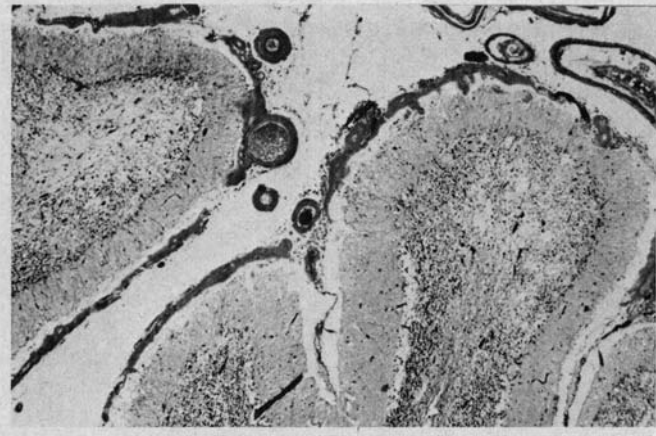


Fig 2.—Case 1. Cerebellar cortex with superficial atrophy and gliosis produced by overlying thickened leptomeninges (hematoxylin-eosin, original magnification $\times 100$).

into hot water without any feeling of discomfort.

Uncorrected visual acuity was 20/25 OD and 20/25+ OS. With refraction only, her left eye improved. Her eyes showed white patches in the posterior fundus suggestive of cotton wool spots and short segments of white vessel sheathing on both arterioles and venules suggestive of a vasculitis. On fluorescein angiography some of these lesions leaked dye. Some of the smaller vessels were tortuous. Over the left disc there was a gauzy haze in the vitreous (Color Fig 1).

The following investigative results were found: proteinuria, 0.05 g/d; no Bence Jones protein; cerebrospinal fluid (CSF) protein level, 0.62 g/L; electrocardiogram, first-degree atrioventricular block; two-dimensional echocardiogram, multigated cardiac scan, and technetium Tc 99m pyrophosphate scan, abnormalities consistent with a diagnosis of cardiac amyloidosis; visual evoked response, P100 latency slightly above the upper limit of normal in the right eye and normal in the left eye; EEG, nonspecific left temporal abnormality; computed tomographic contrast-enhanced scan, low-density area in left temporal region thought to be consistent with an old infarct; nerve conduction studies, bilateral carpal tunnel syndrome, right ulnar nerve slowing, and absent galvanic skin response; and normal brainstem auditory evoked response and somatosensory evoked response. Biopsy specimens of gingiva, fat, and fibrous tissue from the carpal tunnel demonstrated amyloid.

At the age of 52 years, her condition had further deteriorated. At this time, her main complaints were increasing hand and leg weakness, causing an unsteady gait, and poor vision. Additionally, her speech had become noticeably less intelligible because of an enlarging tongue. Vitreous opacities were now seen in both eyes. Bilateral vitrectomies were performed, and the specimens showed amyloid. Her visual acuity subsequently improved from 20/400 OU to 20/40 bilaterally.

Analysis of blood samples revealed the presence of an anomalous transthyretin (prealbumin). Three plasmapheresis exchanges (of approximately 2 L each time) during a one-week period were performed, and transthyretin concentrations were measured (employing a radial immunodiffusion technique according to Mancini et al¹) as shown in Fig 3.

CASE 3.—This patient was the son of patient 2 and nephew of patient 1. He had a history of hemiplegic migraine and seizures in his teenage years. In his early 20s, he had multiple admissions to hospitals with alternating hemiparesis or psychosis.

At the age of 28 years, he was found unconscious at home with a left hemiplegia, decerebrate posturing, and bilateral extensor plantar responses. A computed tomographic scan revealed a large intracerebral hematoma in the right posterofrontal region. A craniotomy and evacuation of the hematoma was carried out, and a biopsy specimen of the brain was taken. Pathological examination of the cerebral cortex and leptomeninges showed extensive amyloidosis in the pia-arachnoid, with the arteries and arterioles thickened by amyloid material.

Soon after the surgery, the patient's condition began to improve and he was able to talk. However, he began to have tonic-clonic seizures and experienced cycles of alternating alertness and unresponsiveness.

Biopsy specimens of the gingiva, sural nerve, and gastrocnemius muscle showed amyloid deposition. A right-sided posterior iliac spine bone marrow biopsy specimen showed focal hypoplasia and interstitial hyaline deposits.

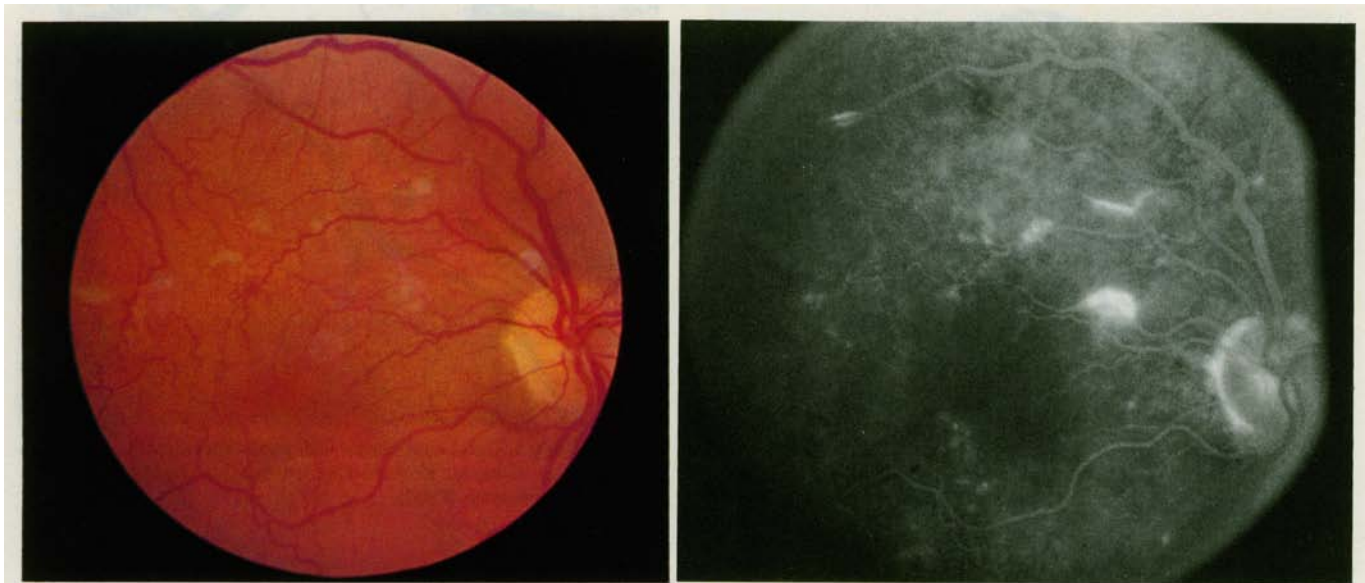
Nerve conduction studies showed diffuse abnormalities that consisted of low-amplitude motor responses, with only mild slowing and normal sensory potentials. A renal ultrasound examination and a two-dimensional echocardiogram showed no abnormalities. Multiple EEGs showed diffuse abnormalities.

The patient continued to suffer from occasional tonic-clonic seizures. He under-

stood verbal commands and would move his right arm and wiggle his toes on the same side. His neck was rigidly extended. There continued to be episodes of unresponsiveness. Finally, at the age of 29 years, 13 months after his intracerebral hemorrhage, he died due to respiratory failure.

An autopsy revealed evidence of early generalized atherosclerosis, acute suppurative pyelonephritis, and acute bronchopneumonia. Histologically, the myocardium disclosed substantial deposition of interstitial homogeneous pink material with fibrous expansion of perivascular areas. This material stained positively for amyloid. Amyloid was also noted within the walls of small coronary arteries and arterioles. Some of the pulmonary vessels displayed focal areas of staining for amyloid. Congo red-positive material was also found in many of the blood vessels of the muscularis externa and submucosa of the alimentary tract. No amyloid was found in the liver. The pancreas showed amyloid deposits in blood vessel walls. The kidneys were grossly sclerotic with many mononuclear inflammatory cells. Amyloid was found in most of the blood vessels of the testes and to a slight degree in the interstitial tissue. There was generalized hyperplasia of the vertebral bone marrow. Amyloid was present in the arteries and arterioles, interstitial connective tissue, and nerve fibers of skeletal muscle.

The brain weighed 1300 g. In most areas, the leptomeninges were yellowish, moderately thickened, and friable; they would break and flake off when attempts were made to strip them from the cortical surface. Coronal sections of the brain showed no gross abnormalities, except for slight uniform ventricular dilatation (Color Fig 2). Several regions of the pia-arachnoid showed thick infiltration by a "sugar-icing" type of material that was yellowish and had a soft consistency. Spongy thickening of the cord's leptomeninges, again with the yellowish brown discoloration, was visible throughout its entire length (Color Fig 3).



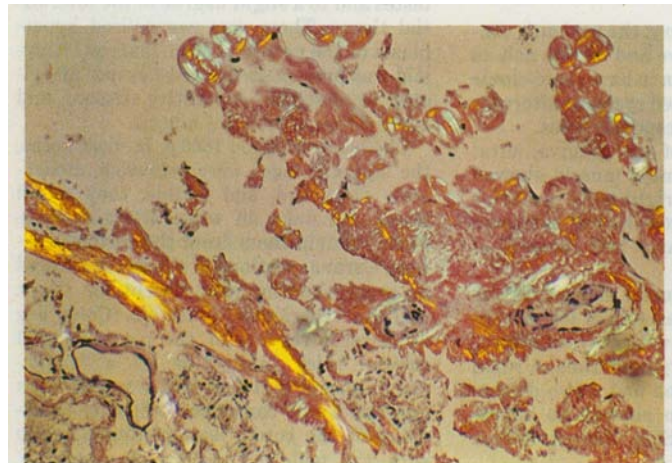
Color Fig 1.—Case 2. Left, Fundus photograph of right eye showing perivascular infiltration of small segments of retinal vessels. Some involved vessels show abnormal configuration. Right, Fluorescein angiogram of view shown at left, demonstrating hyperfluorescence at sites of infiltration.



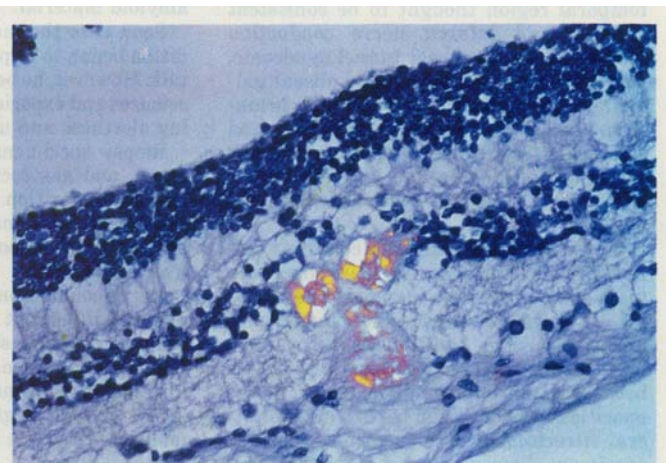
Color Fig 2.—Case 3. Coronal section of brain at level of pineal body showing yellow discoloration of leptomeninges and ependymal surface of third ventricle. (Note plaquelike thickening over right parasagittal cerebral cortex.)



Color Fig 3.—Case 3. External surface of spinal cord showing thickened, yellowish-brown, spongy leptomeninges, especially over lumbosacral segments.



Color Fig 4.—Case 3. Heavy deposits of amyloid in vessel walls and concentric laminae formations around arachnoid trabeculae; latter display phenomenon of "Maltese crosses" under polarized light (Congo red, original magnification X150).



Color Fig 5.—Case 3. Retina under polarized light showing amyloid deposits (Congo red, original magnification X200).

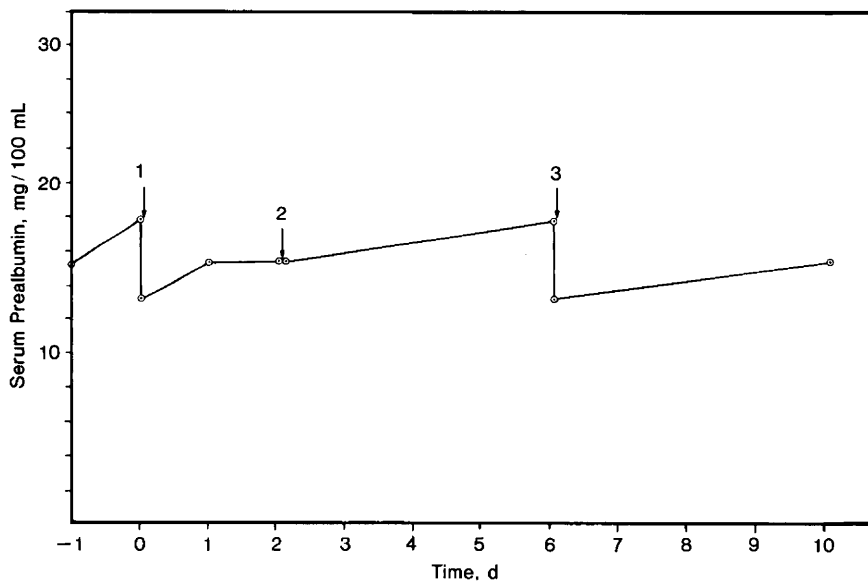


Fig 3.—Case 2. Plasmapheresis effect on concentration of circulating serum prealbumin. Plasmapheresis exchanges were as follows: 1, 2000-mL exchange; 2, 1800-mL exchange; and 3, 2000-mL exchange. Replacement fluid was 5% human serum albumin.

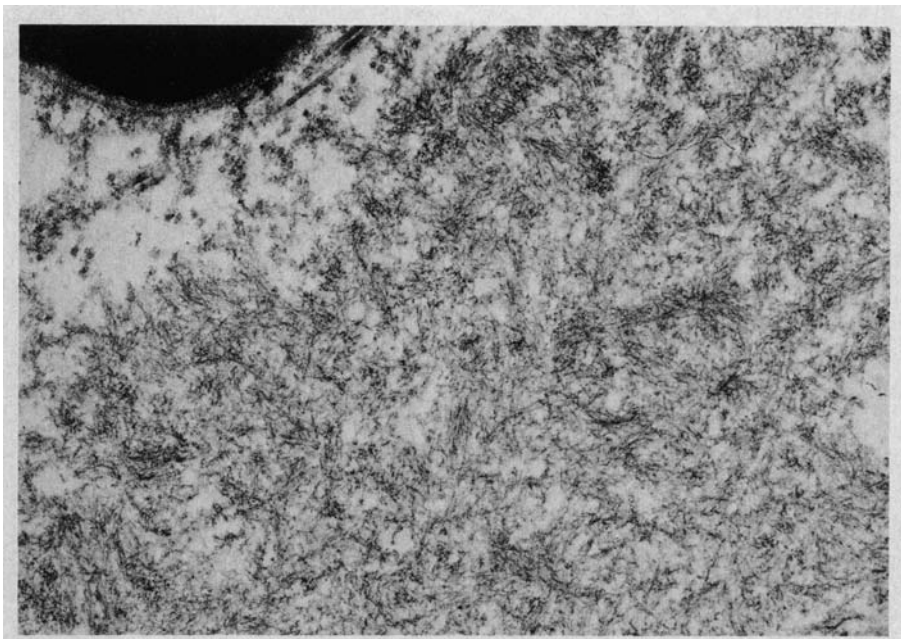


Fig 4.—Case 3. Electron micrograph showing endoneurial amyloid deposit (original magnification $\times 20000$).

Histologically, the thickened portions of the pia-arachnoid overlying the sulci of the cerebral cortex showed a heavy deposit of homogeneous, amorphous, proteinaceous material that was sparsely infiltrated with lymphocytes and macrophages but no plasma cells. This material stained negatively or only palely with Congo red. In other areas, the thickened leptomeninges showed a heavy meshwork of strands and trabeculae composed of acellular fibrillary material that stained strongly positive for amyloid. At all levels of the pia-arachnoid, short strands or plaque-like formations, occasionally with concentric laminae, were

seen that displayed typical amyloid birefringence with Congo red staining under polarized light (Color Fig 4). Electron microscopy demonstrated the characteristic straight, nonbranching amyloid fibrils, with diameters ranging from 5 to 15 nm (Fig 4). All blood vessels within the subarachnoid space were heavily infiltrated by amyloid, but the positive staining extended only a short distance into the cerebral cortex. Medium and large blood vessels in the pia-arachnoid demonstrated amyloid deposition that was limited to adventitial layers of the vessel, with sparing of the intimal and medial layers. The choroid

plexus, including the entire thickness of blood vessel walls, was heavily infiltrated by amyloid. In the spinal cord, amyloid infiltration of the pia-arachnoid was abundant along the subpial surface of the cord immediately under the meninges. The blood vessels about the spinal cord were markedly infiltrated with amyloid but only in the subarachnoid space. There was superficial demyelination of the spinal cord under the soft meninges. Histological examination of the right eye showed the presence of amyloid deposits within the walls of the vasculature and small plaque-like formations within the retina (Color Fig 5).

COMMENT

Three members of an Italian family suffered from neurological disease that involved the brain, spinal cord, and peripheral nerves. Amyloid deposition was found both in the pia-arachnoid and meningeal vasculature of the cerebrum and spinal cord. The pattern of disease in this family was consistent with a dominant mode of inheritance. Both deceased patients had intracerebral hemorrhages. Spinal cord disease resulted from compression by amyloid deposits, hemorrhages, and ischemia. The retinal vessels were also shown to be involved in patients 2 and 3.

Amyloid deposition was not limited to the central nervous system in this family. The bilateral carpal tunnel syndrome in patient 2 was due to nerve compression by amyloid deposition. Vitreous opacities found in patient 2 were shown to be positive for amyloid. Marked tongue enlargement in patient 2 undoubtedly represented amyloid deposition in that tissue. Patients 2 and 3 both showed gingival amyloid deposition, and patient 2 had findings consistent with cardiac amyloidosis. Many other organs were infiltrated with amyloid material as shown in the complete autopsy of patient 3. The majority of the amyloid appears to have been concentrated in the walls of the vasculature.

Familial amyloid polyneuropathy, the most common familial amyloidosis with nervous system involvement, usually spares the central nervous system.⁴ A study of one kinship with familial amyloid polyneuropathy, however, has shown severe thickening of the leptomeninges due to amyloidosis.⁵

The common sporadic variety of cerebral amyloid angiopathy typically affects elderly persons (ranging from 8% at the age of 70 years to almost 60% over the age of 90 years).⁸ Cerebral amyloid angiopathy is not associated with significant systemic vascular amyloidosis.⁹

Familial cerebral amyloid angiopathy has also been documented. Two families, one from Iceland² and one from the Netherlands,³ with members who died at an early age of cerebral hemorrhage, were found to have amyloid deposits in the walls of their cerebral vessels; however, these patients did not have amyloid deposition elsewhere in the body.² It has been shown that the basic abnormality in this patient group is in the metabolism of an alkaline microprotein called "γ-trace," which is found in abnormally low concentrations in the CSF.¹⁰

Three families with oculoleptomeningeal amyloidosis (OLMA) that involved the central nervous system and the eyes have also been described.^{1,11,12} In these families, amyloid deposition was discovered in the perineural vasculature and interstitium of the cranial and spinal roots and ganglia, as well as the subarachnoid vessels, leptomeninges, and under the ependyma. However, intracranial hemorrhage and significant systemic amyloidosis were not seen. The amyloid deposition within the eye has usually taken the form of vitreous opacities.

The family in our study is most similar to the kinships that were described as having familial OLMA. The family shares various features in common with this condition: a domi-

nantly inherited pattern, seizures, periodic obtundation, hemiplegic episodes, sensory disturbances, headaches, vitreous opacities, and extensive amyloidosis of the leptomeninges and the subarachnoid vessels. The family differs in that, while previously described kinships of OLMA were affected symptomatically in the 4th, 5th, or 6th decades, our members were affected during the first and second decades, with two of the three patients dying by the age of 40 years with massive intracerebral hemorrhage. We also found evidence of retinal angiopathy not previously described in other kinships. The family in our study also showed symptomatic evidence of systemic amyloidosis (an enlarged tongue, cardiac amyloidosis, peripheral nerve entrapment syndromes, etc), a feature likewise not reported in previous kinships. While the type of amyloid has not been specified in other kinships, we note the amyloid in our family to be a transthyretin.

Most of the familial amyloids presenting as neuropathies are found to be of the prealbumin or transthyretin type (so named because of its ability to transport thyroxine and retinol). Cerebral amyloid angiopathies have never been shown to have a transthyretin type of amyloid material.

Transthyretin is produced by the choroid plexus and the liver and,

hence, is present in both the CSF and plasma. There has been some discussion as to the source of anomalous transthyretin in familial amyloid polyneuropathy.¹³ We believe that, at least as far as deposits in the pia-arachnoid blood vessels in our cases are concerned, the transthyretin appears to be CSF derived, as both intimal and medial layers of larger caliber blood vessels tend to be completely spared, while adventitial layers are heavily infiltrated. On the other hand, all layers of blood vessels within the choroid plexus are diffusely infiltrated.

Finally, we report an attempt to treat amyloid with plasmapheresis. Unfortunately, this effort to reduce the amount of circulating precursor produced only a short-lived response. Nevertheless, a more long-term plasmapheresis regimen should be carried out before passing final judgment on this mode of treatment. In retrospect, we believe that because the anomalous transthyretin found in the leptomeninges is most likely CSF derived, plasmapheresis would probably not be beneficial in slowing the progression of neurological disease.

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