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Meningioangiomatosis: an immunocytochemical study

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Summary. Meningioangiomatosis (MA) is a rare malformative lesion of the central nervous system. It has generally been thought that the main cells forming this lesion are derived from arachnoidal cap cells. We report a case of MA in which histochemical, immunoperoxidase and electron microscopic studies did not support a meningothelial origin of this lesion. Rather, the lesion in this case appears to be a vascular malformation with the dominant cells being fibroblastic, derived from vessel walls; however, their origin from arachnoid cap cells that differentiated into fibroblast-like cells could not be totally ruled out. Residual neurons within the lesion contained neurofibrillary tangles with ultrastructural and immunostaining properties identical to those seen in Alzheimer's disease except for the absence of A4 amyloid.

Key words: Alzheimer's disease – Immunocytochemistry – Meningioangiomatosis – Neurofibrillary tangles – Vascular malformation

Meningioangiomatosis (MA), first described by Bassoe and Nuzum in 1915 [1] and later named by Worster-Drought and associates in 1937 [31], is a rare disorder thought to be a malformative lesion of the cerebral microvasculature. Although it is most commonly seen in association with von Recklingshausen's disease, several cases have been reported in which the clinical stigmata and family history of neurofibromatosis are absent [11, 14, 18, 21, 23, 24, 27]. A spectrum of histological changes are seen between angiomatosis, in which there is a circumscribed proliferation of thick-walled capillaries confined to the cerebral cortex, as seen in Sturge-Weber disease, and meningiomatosis in which spindled cells proliferate in the perivascular spaces, forming cellular whorls and psammoma bodies reminiscent of meningioma [26]. The leptomeningeal component of some cases of MA consisted almost entirely of what was interpreted as due to proliferation of meningothelial-like cells resembling meningioma en plaque while others were formed almost entirely of angiomatous elements. The presence of neurofibrillary tangles (NFT) in neurons both within and adjacent to the lesion also have been described [11, 21].

The pathogenesis of MA remains unclear. Kasantikul and Brown [14] hypothesized that that the lesion arises form an initial angiomatous component with the meningial elements being incorporated secondarily. Electron microscopic studies, as well as negative staining for S-100 protein [18], have shown that these cells are not derived from Schwann cells. The ultrastructural study of one of the six cases reported by Halper, et al. [11], showed features of meningothelial cells with interdigitating cell membranes, desmosomal junctions and cytoplasmic intermediate filaments; however, they did not elaborate about the frequency of these cells in their material. Immunostains for lectin with *Ulex europaeus* I as well as for glial fibrillary acidic protein (GFAP) and S-100 protein (S-100) have confirmed numerous cortical blood vessels and gliosis but showed no reactivity with the cells in the Virchow-Robin space [11, 24]. Given the light and electron microscopic resemblance of the perivascular cells in MA to meningothelial cells, it has been generally supposed that they are derived from arachnoidal cap cells [26].

We report a recent case of MA in which we undertook histochemical, immunoperoxidase and electron microscopic studies to better elucidate the nature of this lesion as well as to determine the immunocytochemical properties of the NFT associated with it.

Case

A 13-year-old girl, who previously had been well, developed persistent, focal seizures of her right upper extremity. These gradually increased in frequency and severity. Approximately 3

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months after the onset of the focal seizures, the patient experienced a generalized seizure following a Jacksonian march of the right upper extremity.

Past medical history was remarkable only for tonsillectomy. The family history was not suggestive of any herediatry disorders; however, the paternal grandfather was reported to have had a brain tumor and the maternal grandfather a seizure disorder. The general physical exam was unremarkable and did not reveal ocular abnormalities, cafe au lait patches or cutaneous nodules. The neurological exam revealed no focal deficits except for a mild left pronator drift.

Eletctroencephalograms revealed left central spike activity. Computed tomography and MRI scans showed a 3 X 2 X 2-cm mass in the posterior portion of the left pareital lobe involving the cortex. The mass contained areas of calcification and hemorrhage of different ages. Arteriography revealed no abnormal vessels.

The patient was treated with anticonvulsant medication, but her seizures proved intractable after multiple revisons and polydrug therapy. She suffered further episodes of hemorrhage approximately 2 years after the onset of the seizures. Repeat MRI at this time was interpreted as showing the left parietal lesion with surrounding edema and hemosiderin staining consistent with recent subacute hemorrhage.

The patient underwent stereotactic resection of the lesion. At surgery, no adhesions of the dura to the brain parenchyma were noted, but the leptomeninges overlying the lesion were heavily vascularized by abnormal vessels. A 1-cm area of sub-pial, fresh hemorrhage was noted. A firm, calcified lesion with well-defined margins was identified in the paramedian area of the left parietal-occipital region which extended to a depth of 3 cm. The lesion assumed the shape of the gyrus. The patient tolerated the procedure well and was discharged 5 days later with improved seizure control on carbamazepine and valproic acid.

Materials and methods

The resected brain tissue was fixed in 10% formalin. Paraffin-embedded sections were then stained with hematoxylin and eosin (H&E), Gomori trichrome, reticulin, phosphotungotic acid-hematoxylin (PTAH) and Bielschowsky methods.

In addition, immunohistochemical investigations were carried out using standard peroxidase-antiperoxidase or avidin-biotin techniques with appropriate positive and negative controls. The following antibodies were employed: S-100 (DAKO Corporation, Santa Barbara, Calif., 1:100 dilution); epithelial membrane antigen (EMA; DAKO, 1:100 dilution); CAM 5.2 (a cocktail of antibodies raised against low molecular weight keratins – 39K, 43K and 50 K; Becton-Dickinson, Mountain View, Calif., prediluted); desmin (DAKO, 1:100 dilution), alpha-1-antitrypsin (DAKO, 1:10 dilution), *Ulex europeus* agglutinin I (UEA-1; Vector Laboratories, Burlingame, Calif., 1:300 dilution); Factor VIII (DAKO, 1:250 dilution); muscle-specific actin (Enzo Diagnostics, New York, N.Y., 1:4000 dilution); vimentin (DAKO, 1:10 dilution); GFAP (DAKO, 1:200 dilution); Alz-50 [a mouse monoclonal antibody (IgM) raised to basal forebrain homogenates from Alzheimer brain which recognizes tau protein and a protein enriched in Alzheimer brain, A68; 1:5 dilution] [30]; Tau-1 [a mouse monoclonal antibody (IgG1) raised to purified bovine tau protein that recognizes a phosphorylated epitope in paired helical filaments and tau protein; sections immunostained for Tau-1 were performed after incubating the tissue sections in alkaline phosphatase; 1:1 dilution [2, 17]; beta synthetic peptide (BetaSP; an affinity-purified rabbit antibody which was raised to a 28-amino acid synthetic peptide derived from the beta/A4 sequence; tissue sections stained for BetaSP were pretreated with 80% formic acid for 1 h to enhance staining; 1:250 dilution) [9, 15]; NP14 [a mouse monoclonal antibody (IgM) that reacts with a phosphorylated epitope in tau and neurofilament; undiluted [7]; Ab39 [a mouse monoclonal antibody (IgG1) to Alzheimer NFT that recognizes a unique epitope in NFT; undiluted [32]; and ubiquitin (UBQ; an affinity-purified rabbit antibody to keyhole limpet hemocyanin-conjugated UBQ that recognizes both free and conjugated UBQ; 1:250 dilution [19].

For electron microscopy, the tissue was immediately fixed in 2.5% glutaraldehyde, postfixed in osmium tetroxide and embedded in plastic. The sections were stained with uranyl acetate and lead citrate, then examined with an electron microscope.

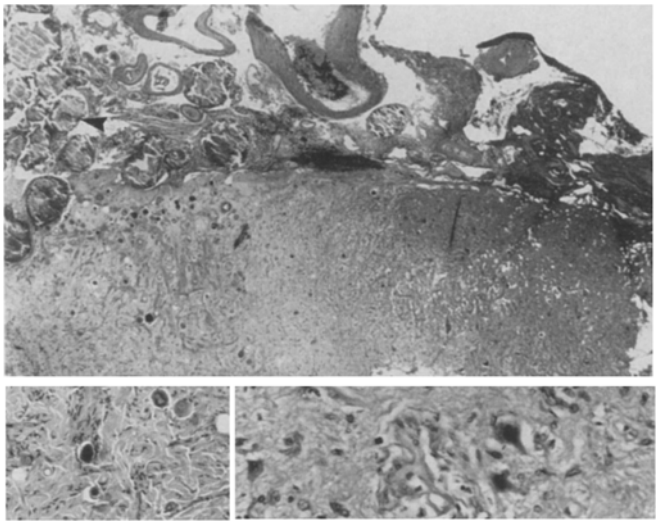

Fig. 1. The lesion replaces the cortical ribbon and is associated with large numbers of abnormal vessels with calcifications (*arrow head*) in the subarachnoid space. The *insert* on the *left* shows a more compact area with numerous calcospheroids superficially resembling psammoma bodies. The *insert* on the *right* shows a looser area displaying neuropil containing several neurons. H&E, × 2.0, *inserts* left × 7.5, right × 15

Results

Grossly, the specimen consisted of several irregular fragments of firm brain tissue which measured approximately 3 cm^3 in aggregate and contained focal areas of calcification. Microscopically, the leptomeninges contained abnormal, calcified vessels which had the appearance of amphophilic or basophilic nodules (Fig. 1). The cortex was replaced by dense, fibrillated tissue centered around capillaries with thick walls. Occasional vessels were surrounded by concentrically arranged spindle cells. In denser areas, many of the vessels were narrowed, hyalinized and often calcified. In looser areas, residual neuropil with occasional neurons was present. Some of the neurons contained NFT. The lesion was rich in reticulin. Bielschowsky stain highlighted the presence of NFT within some neurons, neuropil threads (NT) and neurites within residual neuropil (Fig. 2).

Staining for EMA (Fig. 3a), S-100, CAM 5.2, desmin, alpha-1 antitrypsin, UEA-1 and Factor VIII failed to stain the main cells forming the lesion and the spindle cells in the perivascular spaces. UEA-1 outlined the capillary endothelium and highlighted the vascularity of the lesion. Muscle-specific actin reacted with

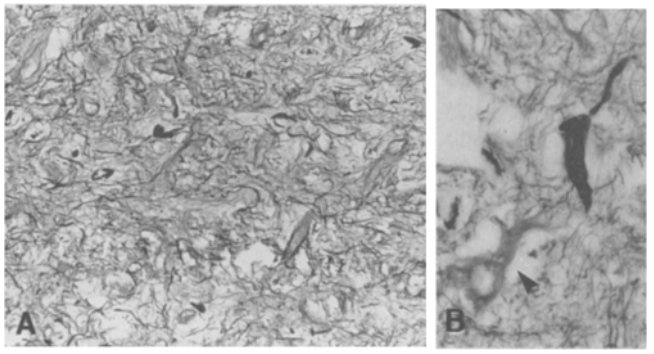

Fig. 2. **A** The lesion is rich in neurites, neurofibrillary tangles (NFT) and neuritic threads (NT). **B** The NT are intensely argyrophilic. A neuron free of NFT is also present (*arrow*). **A, B** Bielschowsky; **A** × 15; **B** × 30

occasional cells as scattered specks contrasting with the stronger reaction of the smooth muscles of larger vessels. The only positive, albeit weak, immunostaining of the spindle cells was for vimentin (Fig. 3b). Although the residual neuropil within the lesion did not demonstrate significant staining for GFAP, the interface between the lesion and the subjacent white matter showed gliosis; the residual neuropil within the lesion did stain with S-100, however. Neurons containing NFT reacted with the Alz-50 and Tau-1 antibodies, which also stained NT (Fig. 4a,b). Reactivity with BetsSP was not demonstrated. NP14 stained both NT and NFT. Ab39 faintly stained NFT but not NT or dystrophic neurites.

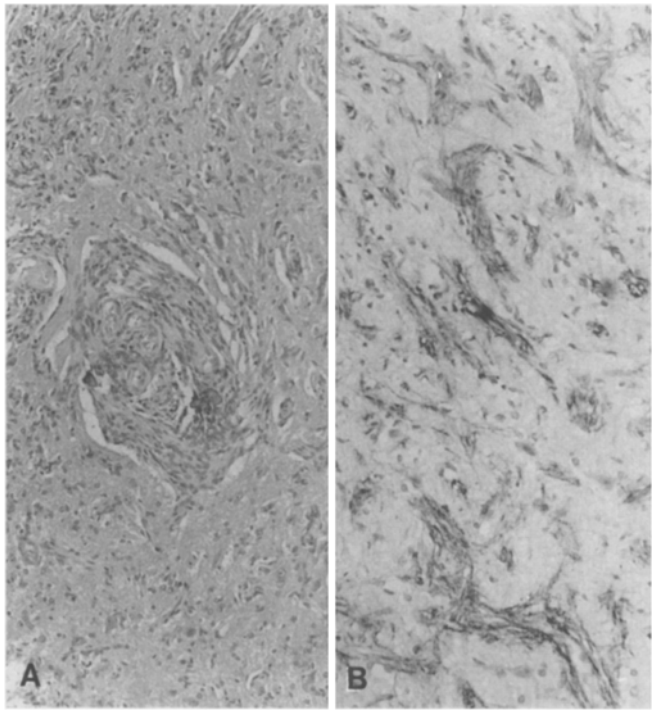

Fig. 3. **A** The perivascular clusters of cells as well as those forming the majority of cells in the lesion do not immunoreact with epithelial membrane antigen. **B** Vimentin showed weak positivity in the main cells forming the lesion. **A** × 10; **B** × 15

Table 1. Results of immunoperoxidase stains

Antibody/antibody to	Perivascular spindle cells	Residual neuropil	NFT	NT	Dystrophic neurons
S-100	–	+			
EMA	–				
CAM 5.2	–				
Desmin	–				
Alpha-1 antitrypsin	–				
UEA-1	–				
Factor VIII	–				
Actin	+/–				
Vimentin	+				
GFAP	–	–			
Alz 50			++	++	–
Tau-1			++	++	–
BetaSP			–	–	–
NP14			+	++	–
Ab 39			+	–	–
UBQ			+/–	+/–	++

S-100 = S-100 protein; EMA = epithelial membrane antigen; UEA-1 = *Ulex europeus* agglutinin 1; GFAP = glial fibrillary acidic protein; BetaSP = beta synthetic peptide; UBQ = ubiquitin; NFT = neurofibrillary acidic protein; NT = neuropil threads

UBQ showed equivocal staining of NFT and NT but stained dystrophic neurites strongly (Fig. 4c), Results of immunoperoxidase stains are summarized in Table 1.

Electron microscopy showed that the cells surrounding the vessels were invested by incomplete basal laminae and collagen. Cells with cytological features of meningothelial cells, especially displaying desmosomal junctions, were rare (Fig. 5). Astrocytic processes were not demonstrated. Neurons containing NFT were packed by intertwining bundles of filaments with a paired-helical arrangement (Fig. 6a). NT consisted of neurites, most likely dendrites distended with paired helical filaments (Fig. 6b).

Discussion

It has been suggested that the spindle cells in the perivascular spaces that make up the predominant feature of MA are arachnoidal. Others have supported the concept that MA is a vascular malformative lesion with the arachnoidal component arising secondarily from the perivascular elements [14]. In the current case, EMA, which is an excellent marker for arachnoid cap cells and a valuable tool in the diagnosis of virtually all forms of meningiomas [28, 29], was not expressed by these cells. Low-molecular weight keratins, for instance CAM 5.2 which is co-expressed in about 10% of all meningiomas, were also not present in these cells. The only clearly positive immunostaining was for vimentin, an intermediate filament protein present in fibroblasts. The results of immunostains and electron microscopy suggested that the large majority of cells in MA were

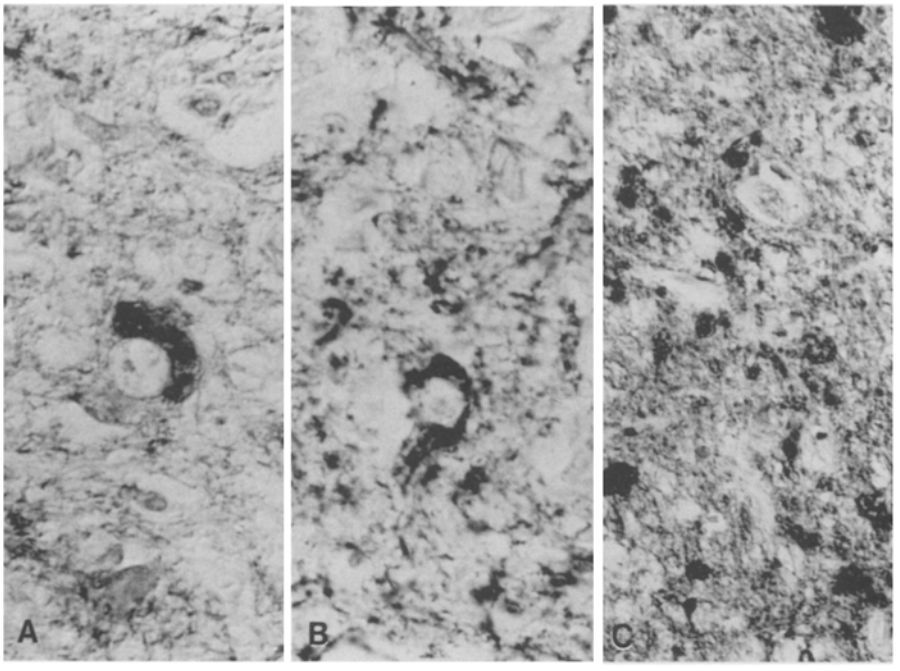

Fig. 4. A Alz 50-positive NFT within a neuron. **B** Tau-1 is expressed by the NFT in neurons and the NT. **C** Ubiquitin reactivity is mainly expressed by the dystrophic axons. **A–C** × 40

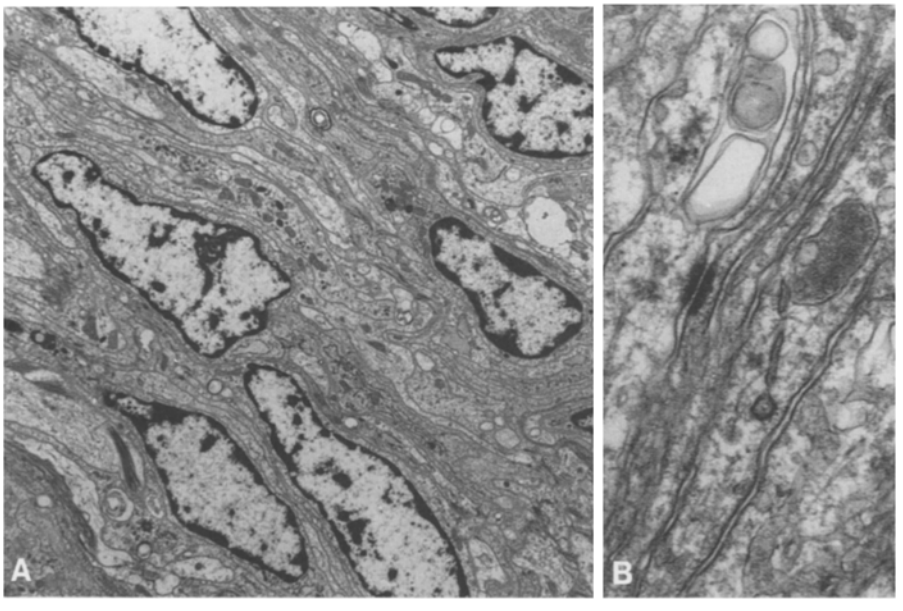

Fig. 5. A Electron microphotograph demonstrating cells with fibroblastic features and incomplete basal laminae surrounding the cells. **B** Desmosomal junctions belonging possibly to entrapped meningothelial cells were rare. **A** × 1,500; **B** × 42,300

fibroblasts, likely derived from vessel walls. Any meningothelial cells present were probably entrapped in the lesion and accounted for the rare desmosomal junctions seen by electron microscopy. These conclusions support the description by Worster-Drought et al. [31] that the condition was a vascular malformative lesion. The presence of clustered, calcified vessels in overlying leptomeninges, which had been noticed in MA by many authors, further support this interpretation. To our knowledge, there has only been one previous study which used an extensive panel of antibodies in MA to elucidate its origin [24]; EMA reactivity was never assessed however. Immunostaining results available on the subject include GFAP, S-100, UEA-1, factor-8-related antigen, desmin and keratin, all of which were negative [11, 18, 24, 27]. Vimentin has been shown to be positive [24]. The assumption that the cells in MA are meningothelial in origin was an impression conveyed by the calcified masses in the leptomeninges, which were interpreted as clusters of calcified meningothelial cells or psammoma bodies [11]. Also, the superficial resemblance by light and electron microscopy of the perivascular cells to meningothelial cells had been a major problem. However, it could be argued that these fibroblast-like cells might have originated from pluripotent arachnoid cap cells that selectively differentiated into a

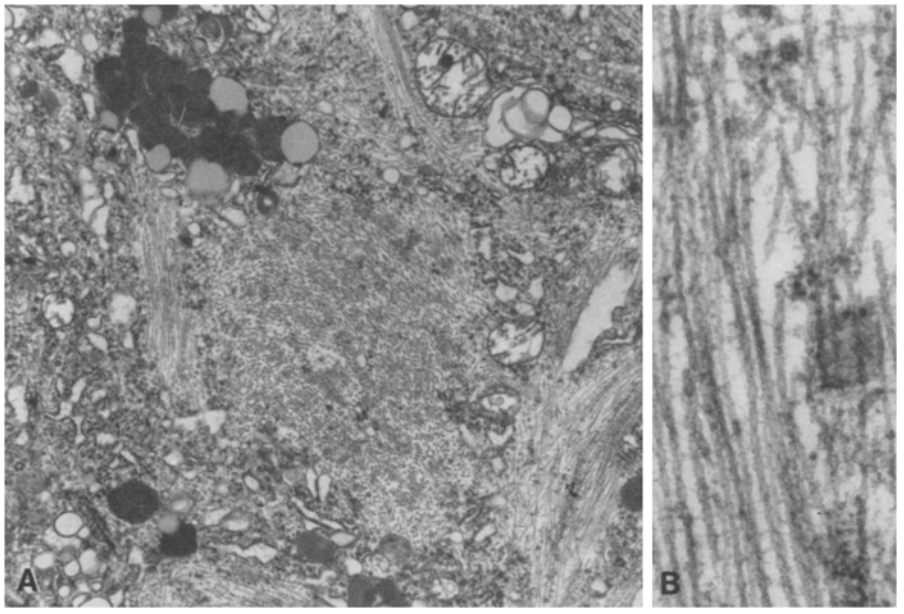

Fig. 6. **A** NFT within a neuron. **B** Paired helical filaments within a NT. **A** × 9,870; **B** × 56,400

fibroblastic cell lineage and this may explain failure of these cells to stain for EMA in our patient as well as in some cases of meningiomas [22]

In H&E-stained sections we could easily identify NFT in some neurons. Immunostaining showed that the neuropil had abundant neurites, rich in neurofilaments, but lacked GFAP-positive processes; the latter were only present at the junction of the lesion and subjacent white matter. Bielschowsky stain confirmed the presence of NFT and a number of NT [4]. The NFT in the lesion showed variable immunoreactivity with several antibodies that are known to react with the NFT of Alzheimer's disease, including Alz 50, Tau-1 and Ab39. These results demonstrate that the NFT in this lesion contain abnormally phosphorylated tau proteins, since Tau-1 only detected the NFT after treating the sections with alkaline phosphatase. The absence of beta/A4 immunoreactivity in the NFT is not surprising, since this immunoreactivity has mainly been detected in extracellular NFT.

A most significant finding was the presence of NT in the lesion, but not in the adjacent brain tissue. NT were described by Braak et al. [4] as a third location for paired helical filaments in the Alzheimer neocortex. NT have been described as a diffuse and laminar alteration of the cerebral cortex in Alzheimer's disease [8, 12, 16], but their presence in other disease processes has not been emphasized and we do not believe that this change has been described in a malformative lesion such as MA. NT are absent from the cortex in diffuse Lewy body disease [9] and they seem to be the pathological feature, along with NFT, that best correlates with dementia in brains with Alzheimer-type pathology [6]. The presence of NT has, however, correlated with the presence of NFT in adjacent cortical areas [25] and, as in the present case, some evidence would suggest that they are derived from dendrites of neurons with NFT [3].

The lesion showed two types of neuritic alterations with UBQ immunocytochemistry. The UBQ antibody reacted with the NT, similar to tau-reactive antibodies such as Tau-1, Alz-50 and NP14, but it also stained granular, irregular structures that have been shown to be most consistent with dystrophic axons [10]. The lesion, thus, displays a spectrum of axonal and dendritic degenerative changes that only differ by their restricted distribution from similar lesions in aging and Alzheimer's disease.

The association of NFT with vascular lesions is not new. Halper et al. [11] observed them in five out of six MA. Liss et al. [20] described them associated with what they called sclerosing hemangioma, but review of this report suggested that the lesion in question was MA. They also recorded high levels of aluminium. Johnson and Nielsen [13] reported three cases of vascular malformations associated with NFT. One of these might also have been a case of MA. The hypothesis proposed to explain this association was that an altered blood-brain barrier leads to excessive deposition of trace elements, as for example aluminium which has been implicated in Alzheimer's disease [5]. It is also possible that serum-derived factors such as unknown proteolytic enzymes may unleash an abnormal metabolism of neuronal fibrillar proteins and may contribute to tangle development.

In conclusion, based on this study, we found little support for the meningothelial origin of the lesion, although we cannot totally rule out that the fibroblast-like cells forming the lesion originated from pluripotent meningothelial cells. We propose that it is most likely a vascular malformative lesion and the dominant cells are fibroblastic, derived from vessel walls. The nature of the residual neuropil, which contains neurons and neurites but no astrocytes, suggests that the lesion, at least in this case, may be considered a "ganglioangiodysgenetic"

lesion. Additionally, the NFT had not only the same ultrastructural features as those seen in Alzheimer's disease but also identical immunostaining properties except for the absence of A4 amyloid.

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