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Neurofibrillary tangles in the dentate granule cells of patients with Alzheimer's disease, Lewy body disease and progressive supranuclear palsy

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Abstract Recent studies have shown that the dentate granular cells of the hippocampus are affected in patients with Alzheimer's disease (AD). To gain a better understanding of the cytoskeletal alterations in these cells, we carried out immunocytochemical and immunoelectron microscopic analysis of the dentate gyrus of patients with primary degenerative dementias, using a monoclonal antibody against paired helical filaments (TG3). This antibody labeled a large number of spherical inclusions in the dentate granule cells of patients with AD and its Lewy body variant (LBV). These inclusions consisted of straight tubular structures (about 18–25 nm in diameter), similar to those found in progressive supranuclear palsy (PSP). These inclusions, although in a smaller number, were also found in demented patients with PSP, but not in those with diffuse Lewy body disease or age-matched controls. These findings indicate that the neurofibrillary alterations in the dentate granule cells of patients with AD, LBV and PSP share cytoskeletal similarities.

Key words Neurofibrillary tangle · Dentate granule cell · Alzheimer's disease · Lewy body disease · Progressive supranuclear palsy

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Introduction

Neurofibrillary tangle (NFT) formation and synaptic damage within selectively vulnerable populations in the hippocampus play an important role in the cognitive alterations in Alzheimer's disease (AD) [19, 24, 34, 39]. Among these populations, the CA1-2 and prosubiculum [4, 21, 22] are regions that display heavy NFT involvement, neuronal or synaptic loss and gliosis, while the CA3-4 and dentate gyrus are generally considered to be less affected [21, 22]. Recent studies have shown that in fact the CA4-dentate gyrus circuitry might be significantly affected in AD and that these alterations might contribute to cognitive dysfunction [39, 52]. Furthermore, lucifer yellow labeling studies of the dentate granular cells have shown that in patients with AD these cells have shorter and less branched dendrites and fewer spines than those from age-matched controls [12]. This indicates that the dentate granule cells might also undergo cytoskeletal neurodegenerative changes similar to the ones observed in other selectively vulnerable neuronal populations.

For a better characterization of the alterations in this neuronal population, we carried out immunocytochemical and immunoelectron microscopic examinations of the dentate gyrus in patients with AD, a Lewy body variant of AD (LBV) [16–18], diffuse Lewy body disease (DLBD) and progressive supranuclear palsy (PSP) [32], using the TG3 monoclonal antibody. This antibody recognizes a phosphate-dependent epitope in paired helical filaments (PHFs) [11, 53] and has been shown to be more sensitive in recognizing Alzheimer-type neuronal pathology than Alz 50 [7, 25, 29, 54].

Materials and methods

Subjects

Thirty-six autopsy cases were used in the present study (Table 1). The criteria for assigning the cases into each of the groups were as follows [16]. AD cases had numerous plaques and NFTs, and presented clinically with dementia but no parkinsonian features. LBV

Table 1 Summary of clinical and histopathological findings in the subjects used in the present study. Values represent mean ± SEM (*AD* Alzheimer's disease, *LBV* Lewy body variant of AD, *DLBD* diffuse Lewy body disease, *PSP* progressive supranuclear palsy, *MMSE* mini-mental state examination, *NA* not available)

$P < 0.01$: * AD vs DLBD; ** AD vs DLBD and PSP; *** AD vs LBV and PSP

	Age at death (years)	Duration of disease (years)	Mental status		Plaques**	Tangles***
			Blessed score*	MMSE score	CA1 (× 1.6 mm^2)	CA1 (× 0.1 mm^2)
AD (n = 11)	78.6 ± 2.4	8.7 ± 1.3	26.5 ± 2.1	7.8 ± 2.1	11.3 ± 1.8	15.0 ± 3.2
LBV (n = 13	78.3 ± 1.5	6.3 ± 0.7	24.2 ± 2.5	8.3 ± 2.6	8.1 ± 1.4	4.1 ± 1.2
DLBD (n = 2)	74.5 ± 0.5	9.5 ± 5.5	8.5 ± 0.5	24 ± 1	0	0
PSP (n = 4)	74.0 ± 3.7	7.5 ± 0.8	18.6 ± 4	19 ± 6	0.2 ± 0.2	0.5 ± 0.2
Control (n = 6)	73.3 ± 3.8	0	NA	NA	0	0

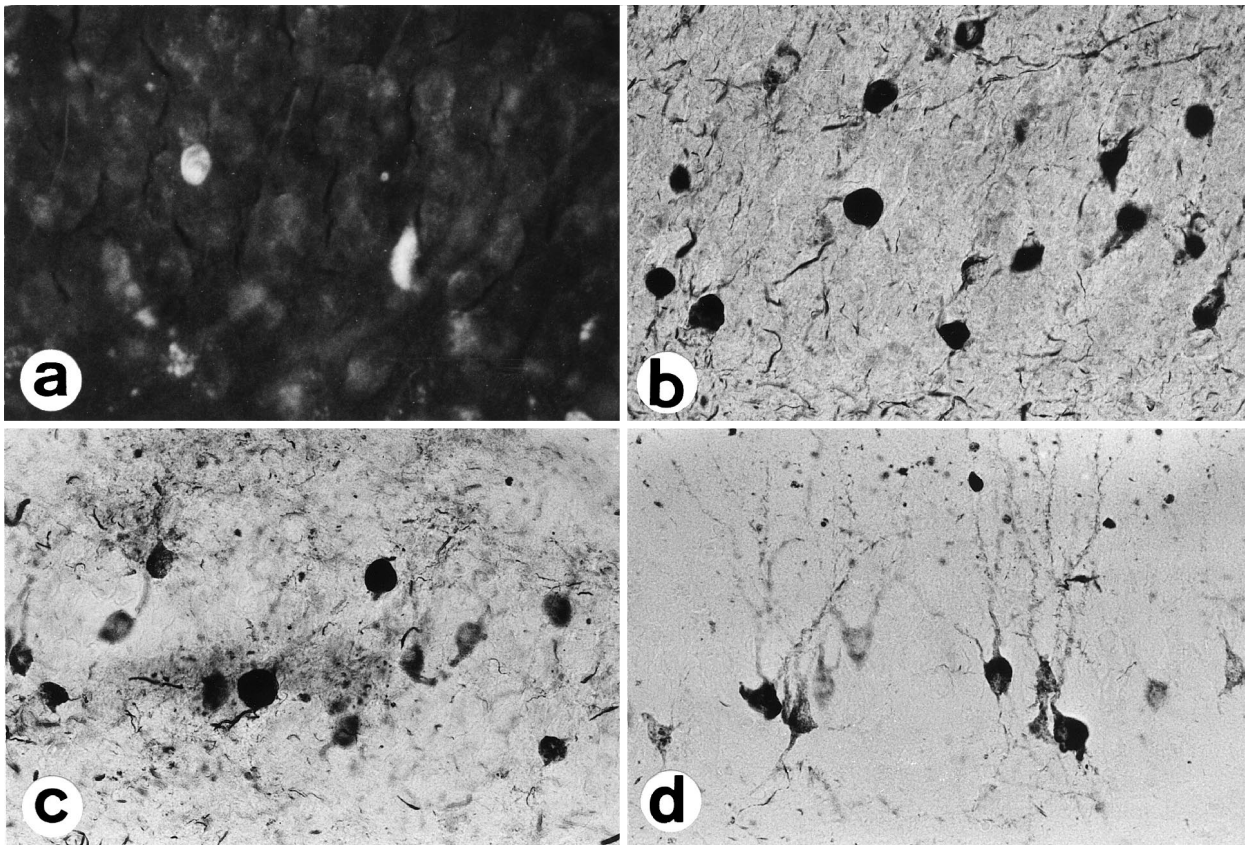


Fig. 1 **a** Neurofibrillary tangles in the granule cell layer of the dentate gyrus of a patient with Alzheimer's disease (AD). Thioflavine S stain. **b–d** TG3-immunoreactive inclusions in the granule cell layer of the dentate gyrus of patients with AD (**b**), its Lewy body varient (LBV; **c**), and progressive supranuclear palsy (**d**). **a** × 530, **b–d** × 300

cases were confirmed by the presence of abundant plaques, occasional NFTs and cortical and subcortical Lewy bodies (LBs); clinically they presented with dementia and subsequently developed parkinsonism. DLBD cases had cortical and subcortical LBs, but did not have either plaques or NFTs; clinically they presented with mild dementia and parkinsonian features. PSP cases were characterized by nigral degeneration and the presence of NFTs in the basal ganglia and brain stem and had no or few ballooned neurons in the cerebral cortex. In addition, three out of the four PSP cases displayed the presence of argyrophilic grains in the limbic system [32]. The remaining six cases were free of clinical and neuropathological and were considered as controls. Mental status was ranked by the Blessed [15] and the mini-mental state examination (MMSE) tests [14]. In each case, blocks taken from the posterior hippocampus were fixed in 2% paraformaldehyde for 72 h at 4°C and the tissues were sectioned at 40 μm with a vibratome. Additional blocks were embedded in paraffin for routine histological examination [48].

Fluorescence microscopy

Paraffin (10 μm) and vibratome hippocampal (40 μm) sections were stained with thioflavine S and viewed with a fluorescence microscope [17, 18, 35]. The entire dentate gyrus was examined and the NFTs counted. Plaques and NFTs in the hippocampus were quantified as reported previously [48]. With this method Alzheimer NFTs and plaques, but not Pick bodies (PBs) or cortical LBs, fluoresced brilliant yellow [17, 18, 35].

Immunocytochemistry

Vibratome sections were immunostained using the avidin-biotin-peroxidase complex (ABC, Vector Laboratories, Burlingame, Calif.)

Table 2 Number of inclusions in the granule cell layer of the dentate gyrus. Values represent mean ± SEM (*NFTs* neurofibrillary tangles, *Thio-S* thioflavine S)

	TG3-positive inclusions*	Thio-S-positive NFTs /40-µm sections*	Thio-S-positive NFTs/10-µm sections**
AD (n = 11)	36.5 ± 10.7	12.0 ± 4.0	1.5 ± 0.2
LBV (n = 13)	10.9 ± 4.7	3.6 ± 1.9	0.5 ± 0.2
DLBD (n = 2)	0	0	0
PSP (n = 4)	5.5 ± 1.6	0.2 ± 0.2	0
Control (n = 6)	0	0	0

*P < 0.03, AD vs LBV and PSP
**P < 0.05, AD vs LBV

method, as described previously [33, 34]. The free-floating sections were blocked with 5% normal serum and incubated overnight at 4° C with the purified TG3 antibody (1:40), followed by biotinylated goat anti-mouse IgM (1:100, Vector). The reaction was visualized with diaminobenzidine (DAB, 0.2 mg/ml) containing 0.001% H_2O_2. TG3 is a monoclonal antibody raised in mice immunized with affinity-purified PHF preparations from AD brain [7, 11, 53]. As previously shown [53], TG3 immunoreactivity was greatly reduced following treatment with alkaline phosphatase, indicating that this antibody is directed against phosphorylated epitopes of PHF. This antibody recognizes NFTs in AD, but does not stain the LBs [7].

Immunoelectron microscopy

Vibratome sections from AD and LBV cases were processed for immunoelectron microscopy as described previously [33]. Briefly, the sections were blocked with 5% normal serum, and incubated with TG3 (1:40) overnight at 4°C, followed by biotinylated secondary antibody (1:200) and ABC (1:200). The reaction was developed with DAB (0.1 mg/ml) with 0.00004% H_2O_2. The immunostained sections were post-fixed in 1% glutaraldehyde for 5 min and 1% OsO_4 in 0.15 M cacodylate buffer, dehydrated in ethanol and embedded in Epon. Ultrathin sections were viewed with a JEOL JEM-100CX electron microscope.

Statistical analysis

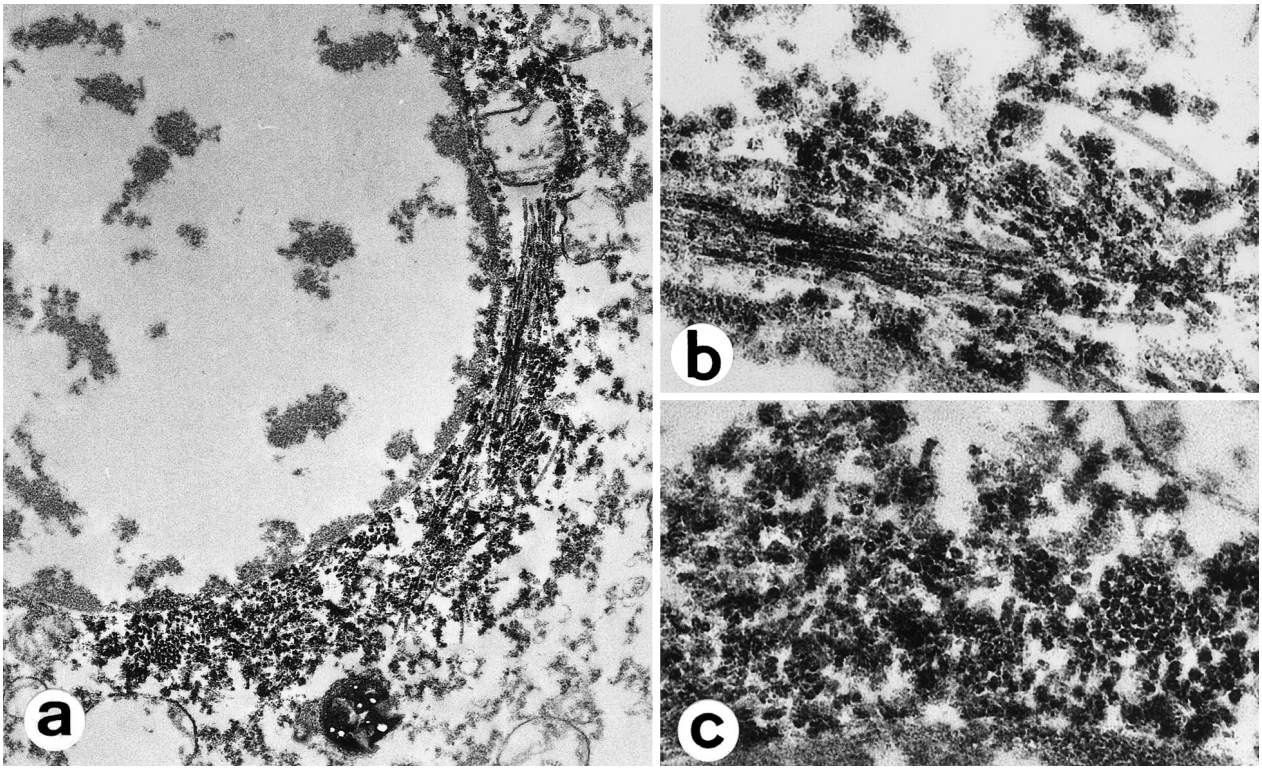
Statistical analysis was done with the STATVIEW II (Abacus Concepts, Calif.) software on a Macintosh personal computer. Comparisons among pathological changes and clinical data were performed with analysis of variance (the control cases were excluded from these latter analyses).

Results

Thioflavine S-positive inclusions

Paraffin-embedded, 10-µm-thick thioflavine S-stained sections showed no or few NFTs in the dentate gyrus granule cell layer. However, 40-µm-thick vibratome sections revealed a significant number of NFTs (Fig. 1a) in 9 of 11 AD, and 8 of 13 LBV cases (Table 2). A few NFTs were also found in one PSP patient.

Fig. 2 **a** Electron micrograph of the TG3-immunoreactive linear inclusion in the dentate granule cell of a patient with AD. **b**, **c** Higher magnification of the same area showing longitudinal (**b**) and cross-sectional (**c**) profiles of the straight tubular structures of about 18–25 nm in diameter. **a** × 13 800; **b**, **c** × 36 000



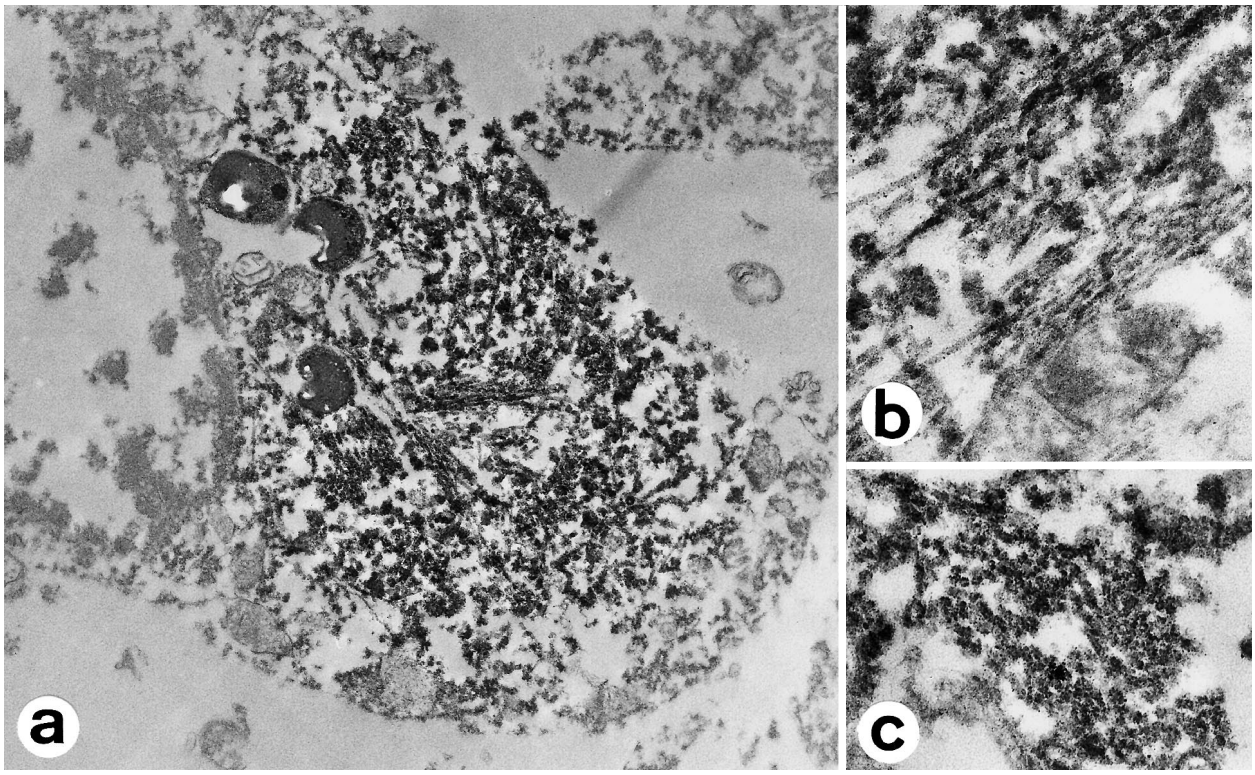


Fig. 3 **a** Electron micrograph of the TG3-immunoreactive globular inclusion of the dentate granule cell in an LBV case. **b**, **c** Higher magnification of another inclusion showing longitudinal (**b**) and cross-sectional (**c**) profiles of the filamentous structures. The constituent filaments are about 25-nm-wide straight tubules. **a** × 13800; **b**, **c** × 36000

TG3 immunocytochemistry

A large number of inclusions in the dentate gyrus granule cell layer of AD (Fig. 1b) and LBV (Fig. 1c) cases were labeled by TG3. These inclusions were usually spherical, and linear inclusions surrounding the nuclei were also observed in 10 out of 11 AD and 10 out of 13 LBV cases. The TG3 immunocytochemistry revealed about three times as many inclusions as the thioflavine S stain (Table 2). These inclusions were also found in all of the PSP patients (Fig. 1d), although on a much smaller scale than in AD and LBV. No inclusions were found in DLBD or control patients.

Immunoelectron microscopy

The dentate granule cell inclusions in both AD and LBV were composed of aggregates of straight tubular structures (about 18–25 nm in diameter) (Figs. 2, 3). The filaments were arranged in parallel fashion and lipofucsin granules were found intermingled with the inclusions, within which no twisted tubules were found.

Statistical comparisons

The number of TG3-immunoreactive inclusions strongly correlated with the duration of disease ($r = 0.632$, $P < 0.001$) and the numbers of NFTs in the dentate granule cells counted in 40-μm-thick ($r = 0.977$, $P = 0.0001$) and 10-μm-thick sections ($r = 0.704$, $P = 0.0002$). The number of inclusions also correlated with the plaque counts in the dentate gyrus molecular layer ($r = 0.776$, $P < 0.002$). However, the number of inclusions did not correlate with cognitive scores or NFT counts in the hippocampal CA1.

Discussion

The dentate gyrus granule cells are generally considered to be resistant to the neurofibrillary alterations associated with AD [21, 22]. However, Dickson et al. [10] reported the occurrence of argyrophilic, thioflavine S-positive inclusions in the dentate granule cells in 17 out of 30 patients with AD, and Kato et al. [26] described similar inclusions in AD. Recently, Braak and Braak [4] observed a large number of NFTs in the dentate granule cells in the brains of patients with advanced AD (stage VI by their classification). In the present study, only a few NFTs were found in the dentate gyrus in 10-μm-thick thioflavine S-stained sections, whereas 40-μm-thick sections of this region contained considerable numbers of NFTs.

Previous immunocytochemical studies demonstrated that the dentate granule cell inclusions immunoreact with anti-PHF [10, 26] and Alz 50 [5]. In the present study, TG3 immunocytochemistry revealed a large number of dentate granule cell inclusions in both AD and LBV. Some

of them resembled PBs, in view of their spherical and compact aspect. The dentate gyrus is well known to contain the highest number of PBs in Pick disease [23] and PBs can occur in AD [3, 42] and LB disease [28], and are labeled by anti-tau and Alz 50 [30, 36], although they are not stained by thioflavine S [23]. Several investigators have reported the occurrence of LBs in the dentate granule cells of patients with LB disease [31, 38, 49]. However, it is easy to distinguish LBs from NFTs, because LBs are not stained by thioflavine S and they do not possess tau [23, 35]. Therefore, we consider that the TG3-immunoreactive inclusions in the dentate granule cells are NFTs and/or pre-tangles.

Ultrastructurally, the TG3-immunoreactive dentate granule cell inclusions were composed of straight tubular structures of about 18–25 nm in diameter. In AD, the NFTs are usually composed of twisted tubules [27, 46, 47]. Although a mixture of twisted and straight tubules has been observed in AD patients [41, 55], in normal cerebral aging [37], and in patients with parkinsonism-dementia complex of Guam [20], they are predominantly composed of twisted tubules irrespective of the site involved. However, Dickson et al. [10] and Kato et al. [26] have reported that argyrophilic inclusions in the dentate granule cells in AD that were composed mainly of straight tubules. On the basis of these findings, it appears that twisted tubule formation occurs only exceptionally in the dentate gyrus granule cell layer.

In the present study, TG3-immunoreactive inclusions were also found in all four demented patients with PSP. In a previous study, Masliah et al. [32] observed that the NFTs in the hippocampi of such patients were composed of straight tubules of about 25 nm in width. Recently, Hof et al. [22] reported the consistent occurrence of NFTs in the dentate gyrus granule cell layer in cases of PSP. Arima et al. [1] demonstrated that ultrastructurally the NFTs in the dentate granule cells in a PSP patient consisted of 15-nm-wide straight tubules. However, Takahashi et al. [44] reported that NFTs in the hippocampus of a demented PSP patient with limbic system involvement were composed almost exclusively of straight tubules. Taken together, these findings indicate that the hippocampus and dentate gyrus may also be involved in the PSP disease process. Furthermore, these findings are consistent with previous studies showing that the cytoskeletal alterations in AD and PSP are to some extent similar [2, 43, 56], in spite of differences in the distribution [51], degree of ubiquitination [2, 6], isoform pattern [8, 13, 40] and ultrastructure [45] of NFTs in PSP and AD. As to the possible mechanisms by which dentate granule cells might develop NFT pathology, it is interesting to note that recent studies have shown that denervation induces abnormal cytoskeletal protein phosphorylation in the hippocampus [50]. In the case of the dentate gyrus cells, denervation might occur as a result of the degeneration of the entorhinal cortex perforant pathway circuitry in AD [4, 24, 34, 39]. This possibility is further supported by the finding that NFTs in the dentate granular cells and plaque formation in the molecular layer of the dentate gyrus were correlated with the number of TG3-immunoreactive bodies in the dentate.

In conclusion, this study supports the contention that the neurofibrillary alterations in the dentate granule cells of patients with AD, LBV and PSP are cytoskeletally similar.

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