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Short communication

Dentate gyrus expression of nestin-immunoreactivity in patients with drug-resistant temporal lobe epilepsy and hippocampal sclerosis

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ABSTRACT

Purpose: Granule cells pathology in dentate gyrus, have received considerable attention in terms of understanding the pathophysiology of temporal lobe epilepsy with hippocampal sclerosis. The aim of this study was to determine the nestin (an intermediate filament protein expressed by newly formed cells), immunoreactivity (IR) in granular cells layers of hippocampal tissue extirpated during epilepsy surgical procedure, in patients with drug-resistant epilepsy.
Methods: Hippocampal sections of 16 patients with hippocampal sclerosis and drug-resistant temporal lobe epilepsy were processed using immunoperoxidase with antibody to nestin. Archival material from 8 normal post-mortem hippocampus, were simultaneously processed. Reactive area for nestin-IR, the total number of positive nestin cells per field (20×), and the MGV (mean gray value) was determined by computerized image analysis (ImageJ), and compared between groups. Student's *t* test was used for statistical analysis.
Results: Nestin-IR cells were found in granule cells layers of both controls and patients. Larger reactive somas ($p < 0.01$) were found in epileptic's sections but a significant reduction in the total number of nestin-IR cells per field and in the MGV was found in granular cells layers of patients with hippocampal sclerosis ($p < 0.01$).
Conclusion: Reduced expression of nestin-IR in granular cells layers of epileptic's dentate gyrus may reflect changes in dentate gyrus neuroplasticity associated to chronic temporal epilepsy with hippocampal sclerosis. Further studies are required to determine the clinical implications on memory an emotional alterations such as depression.

1. Introduction

Hippocampal sclerosis (HS)[1] is the most frequent lesion found in patients with drug-resistant temporal lobe epilepsy (TLE)[2], and its resection eliminates seizures in a 60–80% of the cases [1,2]. Nevertheless, the mechanisms involved in the pathogenesis of HS are still controversial and poorly understood [3].

Despite HS is characterized by pyramidal neuronal loss and reactive gliosis, in the last years researchers have been focused on granule cell pathology dentate gyrus (DG)[3], neurogenesis (NG)[4] and changes in neuroplasticity (NP)[5] with many controversial findings: while a significant increase of mitotic activity in DG was found in acute experimental models of epilepsy [4–6], a reduction of newly formed cells (NFC)[6] have been found in chronic models of epilepsy [7–9] and in patients with drug-resistant epilepsy [10–13]. Furthermore, a reduction in DG NG and NP have been associated to cognitive deficits and emotional disturbances (depression), frequently observed among TLE patients [14,15].

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[1] HS: hippocampal sclerosis.
[2] TLE: temporal lobe epilepsy.
[3] DG: dentate gyrus.
[4] NG: neurogenesis.
[5] NP: neuroplasticity.
[6] NFC: newly formed cells.

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In a previous study, we found a decreased in doublecortin (DCX)[7] immunoreactivity (a marker used to determine NFC in the late stages of NG) in adult patients with TLE and HS [16]. The aim of the present study was to determine nestin immunoreactivity (nestin-IR), an intermediate filament protein expressed in early stages of differentiation of NFC, in granule cells layers of DG obtained from patients with HS and chronic TLE, who underwent epilepsy surgery.

2. Methods

2.1. Patients and samples

Hippocampal sections from patients with TLE and HS who underwent epilepsy surgery (anterior temporal lobectomy) were included in this study. All patients underwent thorough clinical, electrophysiological (video-EEG), imaging evaluation (magnetic resonance imaging – MRI), neuropsychological and psychiatric assessment prior to surgery [17]. Pharmacoresistance was defined as failure to achieve sustained seizure absence (no type of seizures for a period of 12 months, or prolongation of three times the pre-intervention inter-seizure interval, which ever longer), with at least two trials of well tolerated, appropriately chosen, and adequate schedules AED (irrespective of being administered as monotherapy or in combination), to achieve sustained seizure absence [18].

Archival material obtained from post-mortem hippocampus matched by gender and age, free from neurological injury, drug and/or alcohol dependency were simultaneously processed as controls.

This study was conducted with the approval of the Ethics Committee of Ramos Mejía Hospital of Buenos Aires Argentina, in accordance with the Ethical Standards laid down in the 1964 Declaration of Helsinki, and all the subjects submitted informed consent.

2.2. Hippocampal sclerosis diagnoses

2.2.1. Magnetic resonance image (MRI)

Magnetic resonance image (MRI)[8] protocol used was sagittal T1-weighted, inversion-recovery, fluid-attenuated inversion recovery (FLAIR) T1 FFE 3D acquisition, perpendicular to the long axis of the hippocampus and T2-weighted axial, parallel to the long axis of the hippocampus. Diagnostic Criteria for HS by MRI was atrophy, hypointense in T1W and IR, hyperintense in T2W and Flair, and alteration of the internal structure of the hippocampus.

2.2.2. Tissue processing and histopathology diagnosis

Hippocampal samples were studied by a neuropathologist to confirm HS diagnoses and were classified according to Blümke et al. [2] criteria. The surgical piece was fixed in formalin for 5 days. After that, tissue blocks (thickness: 5 mm) were made following coronal planes and were embedded in paraffin. Sections were cut at 7 mm with a microtome, stretched in water at ambient temperature and mounted on slides, deparafined in xylene, hydrated and stained with hematoxylin-eosin, luxol fast blue and thionin stain. Archival material obtained from normal post-mortem hippocampus matched by gender and age, and free from neurological injury, drug and/or alcohol dependency were simultaneously processed as controls.

2.2.3. Immunohistochemistry

After deparaffinizing sections were treated according to the following procedure: a 15-min wash in distilled water, then an incubation in a microwave oven twice for 5 min in a citric acid solution (0.1 mol/L citric acid monohydrate and 0.1 mol/L trisodium citrate dihydrate), pH 6.0; after that a twofold 5-min wash in phosphate-buffered saline (PBS), the sections were incubated for 30 min in 0.5% (v/v) hydrogen peroxide in ethanol to quench-endogenous peroxidases. Afterwards, they were incubated overnight in a humid chamber with mouse monoclonal anti nestin (EMD Millipore) diluted 1:200 in PBS Triton X-100 and 0.1% (w/v) sodium azide. The complex was detected using supersensitive multilink-HRP/DAB kit from Bio-Genex (QD000-5L) following the vendor's procedure. After dehydration the sections were mounted with permount medium and coversliped.

Controls omitting the primary and the secondary antibody were determined.

2.2.4. Image analysis

Immunocitophotometric evaluation and quantification of granule cells layers of DG expressing nestin (nestin-IR)[9] was determined by computerized image analysis. The images were acquired by a SONY. Power Had 3CCD color video camera system from a Zeiss Axiophot microscope. Images were digitalized with a resolution of 768–494 pixels and were analyzed using ImageJ analysis program. All images were captured under identical lighting and magnification conditions. Ten fields per section were evaluated in cases and controls. The total number of positive nestin-IR cells by field (20×), the mean gray value (MGV) and the reactive area (pixel^2) were measured along the granular layers. After shading correction, an automatic discrimination procedure was performed and the MGV of specific labeling and the background was measured. The specific MGV was defined as the difference between the background MGV and the MGV of the discriminated profiles, indicating a measure of staining intensity. Student t test was used for statistical analysis.

2.2.5. Statistical analysis

Student's t test was calculated, $p < 0.01$ was considered significant. SPSS for Windows was used to perform statistical analysis.

3. Results

In this study hippocampal samples obtained from 16 p.[10] 7 women (44%) and 11 men (65%), mean age 38 ± 8 years, with TLE and eight post-mortem controls, age 39 ± 17.4 without pathology, matched by age and sex ($p > 0.05$) were included. Demographic, clinical and histopathological variables are resumed in Table 1.

In both control and epileptic sections, positive nestin-IR cells were found among pyramidal layers, subpial zones, and in granular cells of DG layers.

Along DG layers nestin-IR granular-like cells were localized preferentially in somas in both cases and controls. Positive nestin-IR cells in epileptic's granular cell layers had larger reactive somas. Many of these cells have ectopic localization, and were found into the molecular layers. On the contrary a reduction in the total number of nestin-IR cells per field (20×) and a lower MGV (indicating a reduce staining intensity of nestin-IR) was found in epileptic's granular cell layers ($p < 0.01$) (Figs. 1–2).

[7] DCX: doublecortin.
[8] MRI: magnetic resonance image.
[9] NC: nestin positive cells.
[10] p.: patients.

Table 1a
Clinical and pathological aspects of patients with resistant TLE and HS.

Case number	Gender	Age	Age of epilepsy onset	Time of epilepsy duration	Epileptic focus	Histopathology	Psychiatric History	Memory	AED	Engel class
1	F	28	2	26	R	HS T1, GCD G0	DP/PS	DMVS	CZP, VPA, CL	III
2	F	24	8	16	L	HS T1, GCD G1	DP/PS/T	Normal	CBZ, LMT	I
3	F	41	23	18	L	HS T2, GCD G 1	DP	DMVER	TPM, CBZ, CL	II
4	F	46	17	29	R	HS T1, GCD G 0	Anxiety	DMVS	CBZ, TPM	I
5	M	40	8	32	L	HS T1, GCD G1	NO	Normal	VPA, LMT	I
6	F	44	2	42	R	HS T2, GCD G1	NO	Normal	VPA, CBZ, TPM	I
7	F	41	1	40	L	HS T2, GCD G0	PS	Normal	DFH, CBZ, LVT	N/D
8	M	40	11	29	R	HS T1, GCD G1	PS	Normal	CBZ, LMT, LORA	I
9	M	35	11	24	R	HS T1, GCD G1	NO	DMVER	LVT, OCX	II
10	M	44	1	43	R	HS T1, GCD G1	NO	Normal	TPM, VPA, CBZ	I
11	M	51	8	43	R	HS T1, GCD G2	NO	DMVS	CBZ, LMT	I
12	M	22	12	10	R	HS T1, GCD G1	NO	DMVS	DFH, LMT, CL	I
13	F	51	17	34	R	HS T1, GCD G2	NO	DMVS	DFH, LVT, TPM	I
14	M	40	1	39	I	HS T1, GCD G2	NO	Normal	VPA, CL	I
15	M	39	11	28	R	HS T2, GCD G0	NO	DMVER	LMT, DFH, CBZ	III
16	M	27	5	22	I	HS T2, GCD G1	NO	DMVER	LMT, CB,C BZ	I

F: female, M: male, R: right, L: left, HS T1: hippocampal sclerosis type 1 (neuronal cell loss affected predominantly in CA1 and CA4), HST2: hippocampal sclerosis type 2 (neuronal cell loss affected predominantly in CA1), GCD: granular cell dispersion; G0: grade 0 (normal), G1: grade 1 (dispersed), G2: grade 2 (dispersed and reduced number of cells) according to Blümke et al. [2] criteria. DP: depression, PS: psychosis, T: psychologic trauma, DMVS: visuospatial memory deficit, DMVE: verbal memory deficit, AED: antiepileptic drugs, CBZ: carbamazepine, VPA: valproate, CL: clonazepam, TPM: topiramate, LMT: lamotrigine, DFH: diphenylhydantoin, LORA: lorazepam, OXC: oxcarbazepine, LVT: levetiracetam, Engel class: Engel classification of postsurgical seizure, outcome I–II (good seizure outcome), III–IV (bad seizure outcome) [25].

4. Discussion

Despite nestin expression in the adult brain is also detected in pyramidal cells in the adult neocortex, and in reactive astrocytes following injury, nestin-IR in granule cells of DG may indirectly identifies NFC and marks the NFC which will differentiate into neurons [19–21]. Granule cells pathology DG NG and DG NP have received considerable attention in terms of understanding the pathophysiology of TLE. The process of adult NG is a multi-step process (proliferation, differentiation, migration, targeting, and synaptic integration), that ends with the formation of a post-mitotic functionally integrated new neuron [19]. It has been proposed, that chronic and recurrent epileptic discharges, as occurs in adults patients with a long history of resistant epilepsy affects the granular layers of DG, and modifies the pattern of NFC process in different levels affecting synaptic integration and NP [9].

Nevertheless, there are controversial findings between acute and chronic models of epilepsy. A significant increase of mitotic activity in DG was found in acute experimental models of epilepsy [4–6]. At early time points after acute epileptic insult, DG dramatic increases the production of new neurons (proliferation) and after that, aberrant migration infiltrate into the dentate hilus and molecular layer and integrate abnormally into the CA3 network [5]. On the contrary to these observations, chronic models of experimental epilepsy found that initial seizure-induced neurogenesis returns to the baseline by about 2 months in rats [22] and reaches substantially below the baseline level by 5 months [8]. Furthermore, repeated seizures (more than 10) reduce NG in DG [10] and the number of newly born cells that migrate abnormally into the dentate hilus (i.e., ectopic granule cells) are significantly reduced in older age [23].

Table 1b
Postmortem controls.

Controls	Gender	Age	Cause of death	Time to autopsy
1	F	60	CPT	≤6 h
2	F	23	NET	≤6 h
3	F	26	CB	≤6 h
4	F	25	CPT	≤6 h
5	M	60	CPT	≤6 h
6	M	59	CPT	≤6 h
7	M	24	NET	≤6 h
8	M	36	NET	≤6 h

CPT: cardiopathy, NET: non-encephalic traumatism, CB: critical burns.

Coinciding with these observations, a reduction of NFC were found in patients with chronic TLE, using protein markers witch indirectly detect human DG NG (direct techniques that mark new DNA synthesis are not ethical to use in humans) [19]. A reduction of PSA-NCAM (polysialylated-neural cell adhesion molecule) was found in DG of children with resistant epilepsy [11] and in TLE patients with severe neuronal loss [24], the absence of Ki-67 immunopositive nuclei (a proliferative marker of early stages of NG) and a reduction of minichromosome maintenance protein 2 (mcm2) (a proliferative marker) was found in DG of ELT patients [13] and a reduction of doublecortin (DCX) (late differentiation events of NG) was described in chronic TLE patients [8,9,13,16].

There are still controversies since other authors found no differences in the expression human NG markers [25], or as well found a higher number of mcm2-positive cells, Ki-67 and nestin, suggesting higher NFC determined in earlier stages of NG [26–28]. Nevertheless, to explain these controversial findings it has been proposed that chronic epilepsy acting through time, affects the survival of NFC with a decline in the neuronal differentiation process [29].

In this exploratory study, we found a reduce number of nestin-IR cells with lower levels of nestin staining intensity in granular cells layers of epileptic's dentate gyrus. These findings may reflect a reduced number of NFC and changes in DG NP associated to chronic TLE and HS. A reduced NP in the DG may have clinical consequences, and may be related to memory deficits and depression, which are frequently associated to chronic and recurrent seizures in drug-resistant TLE [2,15]. NFC are reduced in experimental models of depression and antidepressants enhances NG [14,15]. Furthermore a depletion of granule cells, has been related to memory impairment in patients with TLE [2,29]. In the present study, memory deficits were presented in nearly 70% and psychiatric comorbidities in almost half of patients.

Some limitations of this preliminary study must be mentioned. The aim of this exploratory study was to localize and quantify nestin-IR in granular cells of DG of patients with HS, and to compare them with normal tissue. In this work, we cannot rule out if the reduced number of nestin-IR cells are based on an overall reduced number of granular cells, described in HS specially in grade 2 of dentate gyrus dispersion [2], or not. Nevertheless a

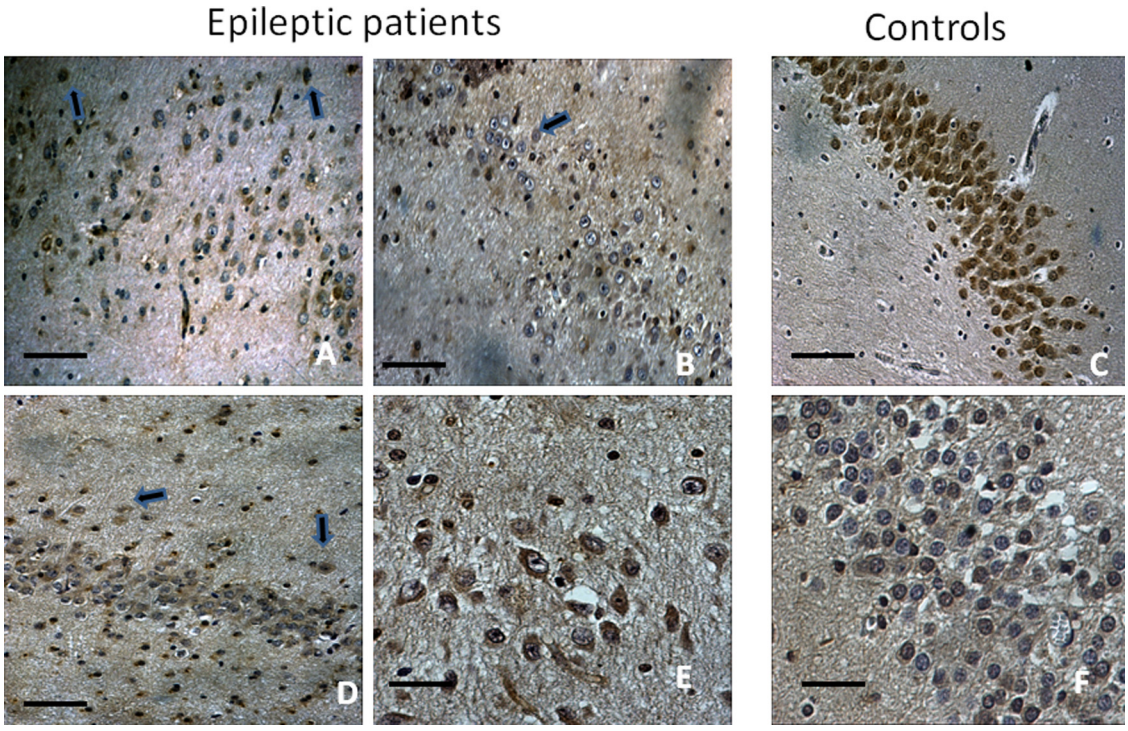

Fig. 1. Microscopy Images of nestin immunoreactivity in dentate gyrus. Optical microscopy images of nestin immunoreactivity (IR) in dentate gyrus (DG) of patients with resistant TLE (temporal lobe epilepsy) and HS (A, B, D, E). Dispersed distribution of nestin IR cells of granular layers and ectopic nestin IR granule-like cells localized into the molecular layer of hippocampus are observed in patients with HS and (arrows in A). Dispersed (A) and focal and segmental distribution of nestin IR cells among granular cell layer in HS (arrows in B) are not observed in controls (C). Ectopic nestin-IR cells into de molecular layer (arrows in D) with larger reactive somas (D, E) are observed in patients with HS. Nestin IR ectopic cells are not seen in postmortem controls (C, F). A reduce in the total number of positive cells and in nestin-IR staining intensity were observed in granule-like cells of patients with epilepsy (A, B, D, E). A–D: low magnification (20×). Scale bar: 60 μm. E–F: high magnification (40×). Scale bar: 30 μm.

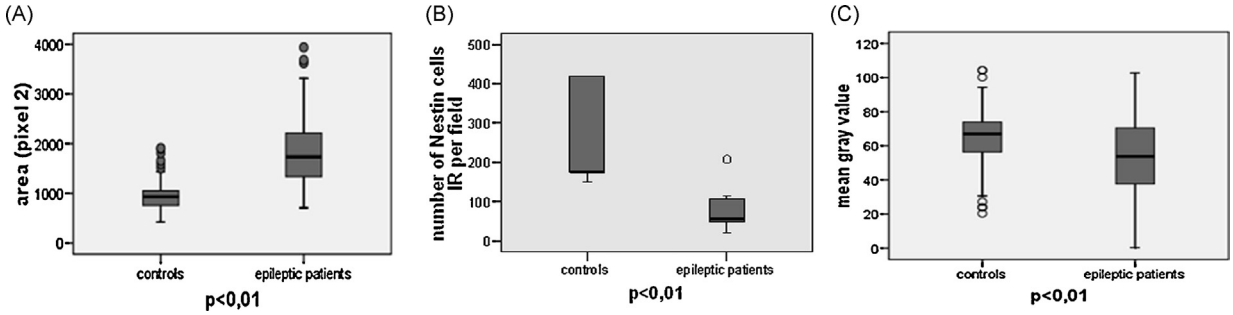

Fig. 2. Quantification of nestin-IR in granular cell layers of dentate gyrus. The measurement of nestin IR area (pixel^2) (mean/error) showed larger somatic reactive area in patients with HS compared with normal controls ($p < 0.01$) (A). The total number (mean/error) of positive nestin-IR cells by field (20×) measured in dentate gyrus was significantly reduced in patients with HS ($p < 0.01$) (B). A reduce in the MGV (mean/error) indicates a lower staining intensity of nestin-IR cells of patients with HS and TLE compared with controls ($p < 0.01$) (C).

decrease in the total number of nestin-IR cells in granular cell layers associated to a reduce in the MGV (a measure of nestin-IR staining intensity), allowed us to think there is a deficit in the mechanisms involved in the formation and/or differentiation of newly formed cells in epileptic's DG. A further analysis using double immunohistochemistry with other neuronal markers must be done in the future, in order to characterize these cells more profoundly with respect to neuronal precursor cells and to confirm these preliminary results. Furthermore, larger studies are required to determine if there is any correlation of these findings with memory and behavioral comorbidities.

Conflict of interest

The authors do not declare any conflict of interest.

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