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Review Article

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Epilepsy as a First Symptom of the Alzheimer's Disease: A Narrative Review

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Abstract

Introduction: Seizures are common in the course of the Alzheimer's disease (AD), but are also described as a first sign of the disease. This work aims at reviewing the literature considering epilepsy as a first sign of the AD.

Method: Medline search until September 2019.

Results: Seizures precede the cognitive deficits in some animal models of the AD. In humans, some case reports and few series reports describe seizures preceding cognitive impairment, with frequency comprised between 1.7% and 3.1%.

Conclusions: The frequency of seizures as a first sign of the AD is probably underestimated. The physician should be aware that seizures of unknown origin among the elderly could be the first sign of the AD. Besides, if confirmed by wider series, it should be admitted the possibility of an atypical non-cognitive onset of the AD.

Introduction

Memory impairment has long been seen as the first sign of the Alzheimer's disease (AD). However, over time, reports of atypical presentation have increased. In 2011, workgroup defining diagnostic guidelines for Alzheimer's disease [1] added non-amnesic presentations to the more typical amnesic presentations, which include impairments in learning and in recalling recently learned information. These non-amnesic presentations include: 1) Language presentation (mainly deficits in word-finding); 2) Visuospatial presentation (deficits in spatial cognition); 3) Executive dysfunction (mainly impaired reasoning, judgment and problem solving). The literature often described non-cognitive symptoms in the early stages of the AD as atypical presentations. For a long time, epilepsy was considered a late symptom, and only quite recently it has been reported in the early stages of the AD, and in the Mild Cognitive Impairment (MCI) [2]. The aim of this work is to review the literature regarding the epilepsy as a first symptom of the AD.

Method

Medline literature until September 2019 was scanned using "epilepsy", "seizures", "Alzheimer's disease", "model of AD", "dementia" and "mild cognitive impairment", as keywords. Other studies were identified by reviewing relevant bibliography quoted in the original papers.

Results

Animal models

Although there are several animal models of the AD, none of these reproduce exactly the human disease. In the Tg2576 mouse the cognitive impairment appears at the age of 3-5 months [3] whereas interictal spikes are found at the age of 5 weeks, before the ß-amyloid deposition, mainly during the REM sleep, spontaneous seizures are observed in older mice [4]. In the same model, Bezzina and Coll [5] found spontaneous interictal spikes and higher seizure susceptibility to systemic injections of GABAa at the age of 1.5 months. The APP23 mice displays spontaneous hypersynchronicity in the hippocampus, beginning at the same age of memory deficits [6]. In the 3xtg-AD mice, higher seizure susceptibility was found at the age of 3 weeks, before amyloid deposition [7], whereas the first cognitive deficit was observed at the age of 3-5 months [3]. Increased sensitivity to pentylenetetrazole was found in the TgCRND8 mice in the pre-plaque stage [8].

Human studies

MCI is regarded as a borderline status between changes of aging and very early dementia. Rao and Coll [9] described unexplained new-onset seizures preceding the cognitive impairment in 10 MCI patients. Vossel and Coll [10] also described 8 MCI patients: In 1 case, the seizures

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Table 1: Studies reporting epilepsy as first sign of the AD.

Author	MCI	AD	Seizures preceding cognitive impairment	Seizures concomitant with cognitive impairment	Generalized	Parzial	Auras
Rao (2009) [9]	10	-	-	-	-	-	-
Picco (2011) [13]	1		1 (1 year)	-	1		-
Vossel (2013) [10]	8	8	1 MCI 1 AD	7 MCI 7 AD	-	-	-
Cretin (2015) [14]	1			1	-	1	-
Cretin (2016) [11]	13 (3.1%)	-	10 (2.7 years)	3	2	11	-
Zarea (2016) [16]	4 (3%)	-	4	-	-	-	-
DiFrancesco (2017) [12]	23 (1.7%)	-	23 (4.6 years)	-	11	5	-
Sarkis (2018) [15]	3		1 (3 years)	2	-	-	3

preceded the MCI diagnosis, and in the other 7 the seizures and MCI appeared at the same time. Studying 430 patients with MCI, Cretin and Coll [11], identified 13 patients (3.1%) with seizures: In 10 MCI patients, seizures preceded the cognitive disturbances by 1-10-years, while in other 3 patients the appearance of seizures and cognitive complaints were concomitant. Analysing 1,371 patients with AD, Di Francesco and Coll [12] retrospectively identified 23 patients (1.7%) with adult-onset epilepsy originating from unknown causes; the seizures preceded the cognitive decline by a mean of 4.6-years. Besides, some case-reports have also been published relatively recently [13-15] suggesting that seizures or auras are preceding or concomitant to the initial cognitive deficits.

Epilepsy is frequent in the familial AD, Zarea and Coll [16], investigating 132 patients with dominantly inherited AD, reported 4 (3%) patients where seizures had represented the first sign of the disease. The results are summarized in the Table 1.

Discussion

According to the criteria developed by NINCDS-ADRDA [17] and Dubois [18], seizures at the onset or very early in the course of the AD make the diagnosis uncertain or unlikely. This statement was removed only in 2011 [1]. It is now clear that seizures are present also in the early stages of the AD, although the causes of this relationship are not clear [2].

Equally, the relationship between the development pace of cognitive impairments and seizures is poorly understood. Indeed patients with seizures in the early stages of the AD have a more rapid cognitive decline [10,12]. The data in the literature are scanty and often obtained from series carried out for other purposes [9,10,16] as a consequence, the frequency of the seizures at the beginning of the AD is probably underestimated, and wider series are needed. Instead, a better understanding of the relationship between epilepsy and AD could provide more insights into the pathogenesis of both diseases, the use of antiepileptic drugs in these patients, and even contribute to the development of new drugs.

These remarks have a twofold value. From a diagnostic point of view, the appearance of seizures of unknown origin in elderly people should raise the doubt of being in the presence of an initial AD. From an analytical point of view, the possibility of an atypical non-cognitive onset, different from those accepted in the guidelines, should be now foreseen, and particularly if the figures below will be confirmed by wider series. This may also apply to other non-cognitive symptoms such as behavioural disorders [19] or eye disorders [20].

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