



Transient epileptic amnesia mistaken for mild cognitive impairment? A high-density EEG study



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ABSTRACT

Mild cognitive impairment (MCI) converts to Alzheimer's disease within a few years of diagnosis in up to 80% of patients. The identification among such a population of a rare form of epilepsy (transient epileptic amnesia [TEA]), characterized by mixed anterograde and retrograde amnesia with apparent preservation of other cognitive functions, excessively rapid decay of newly acquired memories, and loss of memories for salient personal events of the remote past, strongly affects prognosis and medical treatment. Our aim was to define the clinical utility of routine high-density electroencephalography (EEG) in patients with MCI for the detection of epilepsy, especially TEA. Using high-density EEG (256 channels), we were able to single out 3 cases of TEA previously misdiagnosed as MCI in this cohort of 76 consecutive patients with MCI diagnosed at our center. Antiepileptic treatment effectively stopped the acute episodes of memory loss. To our knowledge, this is the first report of an incidence of 4% of TEA recorded in such a cohort.

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1. Introduction

The world's population is growing older. This phenomenon has focused political and medical attention on the elderly and on age-related cognitive decline in particular. Among the elderly, mild cognitive impairment (MCI) affects a proportion of those who will later develop clear-cut dementia, particularly of the Alzheimer's disease (AD) type. Several referral centers have reported a 10–15% annual conversion rate of MCI to AD [1–3], with an 80% conversion rate within 6 years of AD diagnosis according to one study [1].

The search for biomarkers has identified altered levels of tau protein and phosphorylated tau and reduced levels of beta-amyloid 42 in MCI, with a pattern resembling that of AD [4]. These findings need to be interpreted with caution, however. While they indicate that a pathological process resembling AD is present, they cannot predict the temporal course of changes in cognition in patients with MCI.

Recording EEG holds promise for improving diagnostic sensitivity in this population. Although AD has been a key focus of research, recent interest in MCI has led to its inclusion in EEG studies. In longitudinal studies, quantitative EEG analysis showed a progression from MCI to AD [5–9], with a gradual increase in theta and delta power and a subsequent decrease in alpha and beta power, as well as differences in their topographical distribution, with the frontal regions more sensitive to beta modifications and the posterior regions more affected by shifts in theta-alpha rhythms [10]. Although not a routine clinical procedure, EEG is quite often a part of the qualitative evaluation of patients with MCI/AD in order to observe graphoelements other than frequency shifts, i.e., epileptiform discharges. Electroencephalography recordings with a high number of electrodes (256-channel high-density EEG), also over the zygomatic and other scalp areas usually not covered by standard montages, afford higher spatial resolution and potentially increase the yield of abnormalities. Moreover, the higher spatial resolution with respect to other acquisition systems has revived interest in the electrical source imaging (ESI) technique, as it permits a more reliable reconstruction of the signal deep generator by solving the associated inverse problem. Electrical source imaging, through an algorithm calculation, localizes the presumed generator of the observed scalp activity over the gray matter in the brain. So far, ESI has been mainly applied to study epileptic EEG abnormalities [11–14] and only sporadically applied to sleep [15,16].

Relevant in this context is a recently identified epilepsy type, temporal epileptic amnesia (TEA). The principal manifestation of TEA is recurrent

Abbreviations: AD, Alzheimer's disease; BADL, basic activities of daily life; ESI, electrical source imaging; GDS, geriatric depression scale; IADL, instrumental activities of daily life; MCI, mild cognitive impairment; a-MCI, amnesic mild cognitive impairment; m-MCI, multiple domain mild cognitive impairment; MRI, magnetic resonance imaging; TGA, transient global amnesia.

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episodes of isolated memory loss [17–20]. It presents typically in middle or older age, with a higher prevalence among men [21]. TEA is characterized by mixed anterograde or retrograde amnesia or both, with apparent preservation of other cognitive functions. Though in some aspects similar to those seen in the syndrome of transient global amnesia (TGA), unlike TGA, TEA attacks are, by definition, recurrent and brief (30–60 min maximum), whereas TGA usually gives rise to a single episode that lasts for hours. Peculiar to TEA is its occurrence upon waking, occasionally with symptoms suggestive of temporal seizures, such as olfactory hallucinations or orogustatory automatisms during the attack [21]. The attacks usually cease with anticonvulsant treatment. Patients suffering from TEA often report an excessively rapid decay of newly acquired memories [22], as well as a loss of memories for salient personal events of the remote past [23], complicating the clinical picture.

A partial overlap of TEA features exists with the epileptic amnesic syndrome (EAS) [24], a further subtype of temporal lobe epilepsy for which the diagnostic criteria include subtle temporal lobe seizures, often including transient memory dysfunction (epileptic amnesic attacks), memory impairment on standard tests, and response to antiepileptic medication. A normal EEG or nonspecific EEG abnormalities do not necessarily exclude the diagnosis. Patients with TEA and EAS can present to a dementia clinic because of problems with everyday memory and long-term memory loss and deterioration of autobiographical memory, thus meeting the criteria for MCI.

The aim of this study was to determine the diagnostic sensitivity and clinical relevance of routine high-density EEG in a population of patients with MCI with amnesic or multimodal symptoms.

2. Materials and methods

The study population was 76 consecutive patients with a diagnosis of MCI according to the 2004 criteria [25] seen at a secondary dementia referral center. Inclusion criteria were as follows: cognitive impairment described by the patient, relatives, or both; cognitive impairment as measured by means of a neuropsychological test battery (and interpreted in conjunction with the first criterion and the patient's personal history) according to Petersen [25], with criteria defining MCI by using a cutoff of 1.5 or more standard deviations (SDs) below normative means on at least one measure in the neuropsychological battery; no impairment of activities of daily living; and absence of dementia as defined by the Diagnostic Statistical Manual of Mental Criteria [26] (DSM-IV-25).

Evaluation included routine hematological screening (glucose, hematocrit, white cell count, liver and thyroid function, vitamin B12, folate) and neuropsychological testing with the Modified Mental Deterioration Battery (MMDB) [27], which provides a comprehensive assessment of general cognitive status, impact on everyday activities (BADL-IADL), and mood state (GDS). The MMDB includes the following: Geriatric Depression Scale-15, Mini Mental State Examination (MMSE), Rey Auditory Verbal Learning Test, digit span sequences, verbal and semantic verbal fluency tests, colored progressive matrices test, Stroop test, verbal judgment test, multiple feature targets cancellation test, and attention matrices, drawings copy, and cued drawings copy tests. All tests are corrected for age and educational level according to validated tables published with each Italian standardized test version. For our patients, tests evaluating verbal memory were relevant: the Rey Auditory Verbal Learning Test and the verbal and semantic verbal fluency tests. The Italian adapted version of the Rey Auditory Verbal Learning Test [27] consists of a 15-noun word list that the subject has to recall immediately after each of 5 consecutive repetitions and after a 15-minute interval (delayed recall) during which the subject has to be engaged in nonmnemonic tasks (i.e., nonverbal testing that does not interfere with recall). An additional recognition trial is performed 15 min after the recall, with 45 words including the 15 words initially presented from the list plus 30 distractor items. Verbal fluencies are tested by asking the subject to say, within 60 s each

time, as many words as possible beginning with the letters F, A, and S (in this order and consecutively) for phonemic fluency and as many words as possible pertaining to 3 categories of objects (names of car brands, fruit, and animals) for semantic fluency [27]. Verbal fluency scores, as well as the Mini Mental State Examination [28], are then corrected according to the age and educational level of the participant, i.e., adding or subtracting additional digits obtained from a grid [27], incorporating the aforementioned data. Here, the corrections were calculated on the basis of the standard deviations from the mean value of the test scores obtained from a healthy population during the standardization procedure. This correction explains the presence of fractional scores reported in such testing.

Imaging studies with 3-tesla magnetic resonance imaging (3T MRI), with evaluation of morphological changes, and 256-channel EEG were routinely performed (20-minutes recordings). The EEG cap, by virtue of its geodesic tensor structure, spreads out evenly over the scalp, including the zygomatic and the occipital area. During the 20-minutes recordings, the subjects carried out activation tasks (fist opening and closing and hyperventilation unless contraindicated by concomitant pathologies). Since these high-density EEG recordings were obtained as part of a larger study to identify possible biomarkers of a diagnosis shift from MCI to AD (paper in preparation), no further activation procedures (i.e., sleep deprivation or photic stimulation) were performed in this patient cohort. In selected cases, 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) scans were obtained. History was collected at the first visit and then again at referral for high-density EEG. The diagnosis at the first visit was amnesic MCI (a-MCI) in 21 patients and multiple domain MCI (m-MCI) in 55. The patient data were reviewed by two experienced neurologists (ADF and PM) and discussed with the neuropsychology unit personnel (GB and EB), and a final diagnosis was made.

3. Results

High-density EEG detected epileptiform discharges in 4 patients, 3 of whom had reportedly had normal standard EEG recordings.

Patient 1 (male, 75 years), with an otherwise unremarkable medical history, was referred because of a 2-year history of recurrent episodes (once every 1–2 months) of very short-lasting amnesias consisting of lack of recognition of familiar persons or even forgetfulness of his ongoing activity, which he was, nonetheless, able to complete if he was reminded of what he was doing, and word retrieval difficulties, associated with deterioration of subjective episodic memory in addition to the concurrent onset of sudden, brief episodes of gastric discomfort, nausea, and orobuccal automatism. A standard EEG at that time was negative. He was referred to our center because of the persistence of symptoms. Neuropsychological evaluation disclosed a subtle amnesic deficit (a-MCI) (Table 1). Diffuse leukoaraiosis and subtle bilateral mesiotemporal atrophy were revealed by 3T MRI. At a follow-up visit 2 years later, high-density EEG showed the presence of rare right frontotemporal sharp waves (SW) (Fig. 1). The bidimensional representation of the EEG signal on the scalp (500 ms time window) located the abnormalities over the zygomatic leads, with a projection to the inferior frontal ipsilateral areas. Lamotrigine therapy (max dosage of 150 mg/day) completely resolved the symptoms. Following consultation with the neuropsychologist team, a diagnosis of TEA was made. Neuropsychological performance at follow-up testing remained substantially unchanged (Table 1), except for a slight improvement in long-term memory and a mild decline in the semantic verbal fluency domain, which was, nonetheless, within the normal range. Rare slow waves persisted over the right temporal region.

Patient 2 (male, 67 years) developed symptoms 4 months after undergoing coronary stenting for ischemic heart disease. He was referred to our center 1 year after the onset of symptoms which included repeated episodes of anterograde and retrograde amnesia lasting from 10 to 30 min and preceded by brief gastric discomfort “going up my nose”,

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