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Long-term cognitive outcomes in patient with epilepsy

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Abstract:

In contrast to short-term cognitive outcomes, long-term cognitive outcomes (over 5 years) has been scarcely assessed so far. Yet, predicting long-term outcomes at any time point of the epilepsy, from initial diagnosis, to medically intractability is very important for therapeutic decision-making, patient information, and orientation. Assessing long-term cognitive outcomes in patients with epilepsy would ideally require longitudinal studies and a comparison with a healthy controls group. This issue has been addressed extensively, but with controversial results. However, there is a general consensus about the fact that cognitive outcome is not the same in all groups of patients with epilepsy. Possible prognostic factors include age at onset, duration of epilepsy, syndrome and etiology, seizure outcome and therapeutics. The multiplicity of factors makes it very difficult to assess their relative weight in individuals. Although long-term cognitive outcome studies are scarce, this issue has been specifically studied in newly diagnosed epilepsies and in focal drug-resistant epilepsies. In the first clinical setting, i.e. newly diagnosed epilepsy, it appears that cognitive deficits are already present at epilepsy onset in a significant proportion of patients but seem to remain stable over time. In focal drug-resistant epilepsies, cognitive deficits (mainly verbal memory) were generally shown to remain stable provided that seizures were controlled either by medication or by surgery. Beyond the possible correlation between seizure and cognitive outcome, no causal link however has been demonstrated between these two important outcomes.

Key Words: cognition – cognitive impairment – epilepsy – long-term

1. Introduction

Epilepsy is one of the most common chronic neurological disorders. According to ILAE's definition, "*epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition*" [1]. Cognitive impairment is often reported in patients with epilepsy (PWE). The prevalence of cognitive disorders is up to 70% of adult patients at disease onset [2]. Several factors may have an impact on cognition such as characteristic features of the epilepsy (epilepsy syndrome, age of onset, disease duration, seizures/interictal activities), sleep quality, brain development in children, brain aging in adults, antiepileptic treatments (drugs, surgery) and etiology [3].

Long-term cognitive outcomes have not been clearly assessed so far in PWE. In temporal lobe epilepsy (TLE) a cross-sectional study reported verbal memory scores with a large cohort of patients [4] ranging in age from 6 to 68 years (1156 patients). The results suggested a major impact of the initial neurodevelopmental disease as well as a negative effect of the interaction between memory impairment and cognitive aging, rather than a gradual decline towards dementia in patients with chronic TLE. During childhood, and even more so in the decade following puberty, the normal development of episodic memory is crucial. The occurrence of focal TLE during this period increases the risk of memory deficit later, even in the absence of an accelerated decline. This robust study reported crucial information but the design was not longitudinal. Longitudinal study of long-term cognitive outcomes in epilepsy is methodologically very challenging, due to missing data, the time course of epilepsy (number of seizures, antiepileptic drug, surgery) and controlled interval test-retest (with reliable change index or healthy controls sample). Moreover, the period of time covered by "long-term outcome" is not clearly defined. Thus, in literature there is wide variability in follow-up duration, ranging from 2 to 15 years.

This article focuses on long-term cognitive outcomes in new-onset epilepsy and focal epilepsy in adult patients with over 5 years follow-up.

2. Newly diagnosed epileptic patients

Studying cognitive outcome in newly diagnosed epileptic patients is relevant because the baseline performance measured before antiepileptic drug (AED) introduction can be used as a reference. This allows differentiating the impact of the etiology (or initial hit) from the impact of seizure recurrence, for example, in the cognitive outcome. Indeed, several studies have

shown that cognitive deficits are already observed in newly diagnosed epileptic patients [5]. Deficits at the very onset of epilepsy and before AED treatment are frequent and mostly affect the domains of attention, executive functions and memory [6-8]. To the best of our knowledge, there are only two papers that focused on the long-term cognitive outcome of this particular population [8,9] with a mean follow-up of 5 years. One study derived from the SANAD study on all types of epilepsies and the other one focused on left TLE. However, even in the first study, a great majority of patients had in fact focal-onset epilepsy (84%) and only 8% had generalized-onset epilepsy. The second advantage of this kind of study is to be more representative of the real population of epileptic patients with a majority being seizure free (58%) and under monotherapy (80%) at last follow-up. The cognitive evaluation was comprehensive and comprised psychomotor speed, memory, information processing, mental flexibility and mood [9]. At baseline, 53.5% of patients had at least one abnormal score (< 2 standard deviation) compared to 20.7% of controls mainly in the same two cognitive domains (memory and psychomotor speed). *“At the 5-year follow-up the majority of cognitive measures remained stable, although significant (but subtle: 10-15% from baseline) declines were noted for memory and psychomotor speed domains in 38% of people with epilepsy”* [9]. The authors did not identify any predisposing factor that differentiated the decliner from the non-decliner. The absence of a healthy paired control group does not allow differentiating the effect of normal aging from a specific effect of epilepsy. The second study was conducted with 20 patients and 46 healthy controls and was focused on verbal memory in newly diagnosed left TLE [8]. It did not show any deterioration over time in verbal memory performance whereas verbal memory impairment was in fact reported early in the course of the disease, at the first neuropsychological assessment. Although these two studies apparently yield slightly different findings their common message is the greater importance of the initial cognitive deficits that clearly exceeds the effect of treatment, seizure repetition, and psychosocial factors over a 5-year follow-up. Does this observation remain true after a much longer disease course?

3. Focal epilepsy

Twelve studies have been recorded on longitudinal neuropsychological follow-up in adult patients with focal epilepsy over 5 years [10-21]. Nine studies focused on TLE and the mean follow-up duration was 11 years. There are five retrospective studies and four prospective studies which included a total of 395 operated and 214 non-operated TLE patients (n=609). Only one cohort included healthy controls [13,14]. Most studies focused on postoperative

outcome but four studies explored long-term cognitive outcome of PWE who had not undergone surgery [18-21]. Normative data was the most common method used with group analyses in all studies but some studies used in addition reliable change index and carried out individual analyses [11,14,16]. The main cognitive domain explored was episodic memory. Other cognitive dimensions (intellectual efficiency, attention, executive functions, processing speed and language) have been less reported and differed according to the studies.

3.1 Memory

Cognitive outcomes after TLE surgery, mainly in memory and language, are a priority in medical care. Short-terms outcomes are well established, and reports have consistently shown that memory and language decline may be observed early after temporal lobectomy [22]. But very long-term cognitive outcomes (10 years and more) in memory are poorly detailed with less than 10 studies (see Table 1).

Verbal memory and non-verbal memory were assessed in all studies but methodological variability makes it difficult to summarize all data. The first study that assessed patients on a very long term was published in 2003 [10]. The mean duration of follow-up was 12.8 years. Authors reported a long-term continuous decline in memory, especially verbal memory, after temporal lobectomy in case of a healthy hippocampus on pre-surgical magnetic resonance imaging scan or a high early post-operative memory score. In other studies, the picture seems to be more complex. In a much larger longitudinal cohort study [11], the authors reported a decline of memory in 60% of patients after temporal lobectomy compared to 50% in the non-operated group of TLE in the long-term follow-up (4.8 years in average). This decline was anticipated on early post-operative assessment in the surgery group. It is however important to note that this decline was more severe in case of left temporal surgery and surgical failure (post-operative recurrence of seizures). In contrast, as compared to patients in the medical treatment group, patients free of seizure after surgery recovered non-mnesic functions one year post-operatively and mnesic functions on a longer follow-up. This is an important finding suggesting that the cognitive decline may be reversed in refractory focal epilepsy by a therapeutic intervention, provided that it is successful on seizures. Another study [17] on a much smaller cohort (25 patients) supported this finding and emphasized the individual heterogeneity of cognitive outcome showing for example that at early (2.7 years) post-operative assessment 12-29% declined (according to the domain of memory) as compared to a control group whereas 8-21% actually improved and that the performance of the whole surgical group tended to evolve towards the pre-operative state at the late assessment (9.8 years in average) with 0-12%

decliners and 0-16% improvers. Predictive factors of decline were normal pre-operative performance, pre-operative cognitive deficit consistent with a contralateral temporal dysfunction, lack of mental reserve, recurrence of seizure, healthy hippocampus and late surgery. The role of seizure persistence in the long-term cognitive decline has remained controversial so far, but with supporting evidence having the advantage (pros: [11,12,16] for example; contras: [13,14]). In contrast, there is a general consensus about the following statements: *i*) memory decline is generally observed after dominant temporal lobe surgery; *ii*) when present, memory decline occurs early after surgery; *iii*) on a long-term basis, there is generally no additional and delayed decline; *iv*) and there is a general trend towards stability as compared to early post-operative assessment and even a possible recovery, especially in seizure-free patients [12].

These results however should be taken with caution according to some authors because many patients had a pre-existing impairment in verbal memory before surgery and neuropsychological testing could not provide evidence of postoperative decline due to the pre-existing low scores [16]. Interestingly, the duration of epilepsy before the first pre-surgical assessment in these studies ranged between 16 and 22 years. It is impossible to determine from these studies whether the pre-operative verbal memory decline observed in left TLE is related to the etiology and is present at the onset of the epilepsy or results from the very long duration of refractory epilepsy before surgery.

Beyond the surgical context (see Table 2), two studies reported a relative stability of memory (verbal and nonverbal) after a decade of follow-up [20,21]. One study using group analysis reported a stability in verbal memory but a decline in nonverbal memory [19]. A study focusing on severe intractable epilepsy in patients living in specialized institutions or referred to a tertiary center reported a decline in verbal memory and identified several predicting factors such as the frequency of generalized tonic-clonic seizures and of complex partial seizures, as well as the occurrence of per-ictal head trauma [18]. In these studies, there was no differentiation by type of epilepsy or the laterality of the seizure focus. Thus, results are few and disparate in PWE who have not undergone surgery.

3.2 Non-memory functions

Long-term follow up in other cognitive domains in a context of surgery has been reported in six studies [10-13,16,17].

Cognitive performances remained globally stable after 13 years on executive function and attention (assessed by a mental control task and a trail making test) [10]. An improvement is reported in two studies [11,12] solely in seizure-free patients, with benefit being greater in operated than non-operated patients [12]. In these studies, executive function was assessed by a word fluency task [11,12] and an inhibition task [12]. Attention was assessed by a cancellation task [11]. These results are in accordance with a meta-analysis of short-term cognitive outcomes after TLE surgery which highlighted a decline or an improvement in these functions [22].

One study investigated long-term outcome in language with Wechsler subtests (Vocabulary and Similitudes) and did not observe any change [10]. These tasks assessed semantic memory, but not naming. None of these selected studies assessed visual naming. This is surprising because in short-term outcomes the prevalence of decline in visual naming after TLE surgery has ranged from 25 to 60% [22].

Moreover, three studies investigated intellectual efficiency and reported less improvement of intellectual quotient in non-dominant but not in dominant TLE as compared to controls [13], improvement in seizure-free patients [17] or stability [16].

Beyond the surgical context, cognitive performances of patients were stable [19-21] except for patients with severe intractable epilepsy who declined in all assessed cognitive domains [18]. Thus, very long-term non-memory function outcomes are poorly detailed and often not statistically analyzed but tend to be globally stable in seizure-free patients, especially after surgery.

3.3 Depression

Depressive symptoms are often assessed in the surgical context or in the progression of the disease in relation with seizure outcome [23,24] but it is rarely studied in relation to cognition and even more in long-term outcomes [25]. In cognitive outcome studies, there is a tendency to exclude patients with mood disorders so it is difficult to know the impact of depression in long-term follow-up. This is surprising considering that the prevalence of depression in PWE ranges from 10 to 60% [26,27]. Only one study reported depression in correlation with cognitive scores [19]. Authors suggested that patients could have better scores in memory tests after a decade of follow-up when mood status improves. In addition, seizure control after epilepsy surgery was associated with improvements in mood and anxiety symptoms [24]. Thus, at long-term follow-up, better cognitive and mood outcomes seem to be related to seizures freedom.

4. Limitations

So, studies of cognitive outcomes in a long-term follow-up are scarce. Here, we have focused on cognitive outcomes over 5 years.

Methods have differed across studies, comparing either operated patients to non-operated patients and/or patients operated on left versus right. The presence of a healthy control group is also quite rare in longitudinal follow-up [13,14]. Group analysis is the most widely used method but some studies tend to use individual analysis and reliable change index [11,14,16]. This type of analysis should be definitively favored because of the individual heterogeneity of long-term cognitive outcome (ranging from decline to improvement).

The neuropsychological assessment has been performed with a wide range of tools which makes it difficult to extrapolate reported results in all patients. One study used story recall for memory assessment and another a word list recall which does not involve the same learning processes. Moreover, normative data differ for each test and authors choose the z-score they consider a cut-off for a pathological score. The reference was set at 1 standard deviation for some and 1.5 or 2 standard deviation for others. This issue is also present in the manner in which cognitive decline is defined (particularly post-operatively).

Some studies did not fully describe their samples [10,12,15] and others included acquired injury/tumor/other pathology in their samples (up to 45% of the sample in one study [11]; [16,18]). The other studies clearly mentioned that patients with other pathologies and/or severe disorders (postoperative complications for example) that could interfere with cognition were excluded [17,19,20]. Tumor is an insidious pathology and we can assume that the mechanisms of epilepsy are different between these two populations so the follow-up cannot be the same.

All selected studies concerned young patients except one that conducted a descriptive analysis [15]. Median patient age was around 30 years at baseline and 40 years at long-term follow-up. At the fifth decade, normal changes in memory are reported in the healthy population [28,29] so it is important to conduct a longitudinal follow-up over 10 years. We already mentioned that there is no study with a follow-up longer than 5 years in PWE newly diagnosed and even less in older patients. This is unfortunate because new-onset epilepsy may be associated with cognitive decline leading to an incorrect diagnosis of dementia in these patients [30]. No more than 10% of new-onset epilepsy cases in older patients involve neurodegenerative disorders [31].

Finally studies with a long-term follow-up on cognitive outcomes are methodologically difficult due to the great variability of etiologies, electro-clinical syndromes and therapeutics [12]. All these reasons, (heterogeneity of neuropsychological assessment, heterogeneity of methodological assessment regarding the presence of a healthy control group and statistical analysis, heterogeneity of timing at the onset of follow-up), make it difficult to extrapolate results of a particular cohort to a whole population. This helps us to understand why study designs are often retrospective in order to form large cohorts that have allowed us to monitor long-term cognitive outcomes in PWE.

5. Conclusion

Through the selected studies we notice that memory remains the most studied function, other cognitive functions are almost always ignored. It appears that shortly after surgery there may be a greater decline of memory performance in left than right TLE patients and a trend to stabilization or even recovery at very long-term outcomes. A possible recovery in seizure-free patients is a major point and patients shall be informed of this possibility. The results for non-memory functions are too few to lead to a consensus. For all cognitive functions assessed, a cognitive baseline is essential to avoid misinterpreting changes in patient outcomes.

Although studies linking depression and cognition in epilepsy are rare and required, there appears to be a relationship with an improvement in memory in long-term outcomes after surgery when mood improves. Early assessment and treatment of depressive disorders in PWE is therefore essential.

Assessing long-term (over 5 years) cognitive outcomes in patients with epilepsy would ideally require longitudinal studies, a comparison to a healthy controls group and an individual analysis (integrating reliable change index) to take into account the great individual variability. This variability depends on multiple factors. Among these factors, the etiology and the repetition of refractory seizures have been emphasized. Three different models have been incompletely explored: in the first model, etiology (brain damage for example) causes both epilepsy and cognitive decline. In the second model, the repetition of seizures causes brain damage which results in cognitive decline (the best example is the status epilepticus). In the last model, the etiology causes seizures whose repetition when refractory causes cognitive decline. The complexity comes from the fact that these three distinct models may in fact co-exist in the same patient depending on the etiology. The best and most extensively studied example is medial TLE with hippocampal sclerosis: an initial status causes brain damage that in turn causes both

seizures and cognitive deficit, which may then be aggravated on a long-term basis by the repetition of drug-resistant seizures.

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Table 1. Long-term cognitive outcomes in memory in temporal lobectomy

Authors	Year	Patients	Healthy controls	Design	Follow up duration	Neuropsychological battery	Long term results
Rausch et al., <i>Retrospective study</i>	2003	52 Left TLE : 21 Right TLE: 23 NO : 8	0	T0= pre-operative T1 = 1 year post-operative T2 = long term post-operative	Range to 9 - 19 years Mean = 12.8 years	Verbal memory : WMS (words list and associative learning, story) Nonverbal memory : WMS (visual reproduction) <u>Normative data used</u>	Comparison % patients < 1 standard deviation : T0 versus T1 versus T2 Left TLE : significant decline in total memory Right TLE: significant decline in total memory Left TLE < Right TLE
Helmstaedter et al., <i>Prospective study</i>	2003	249 Left TLE : 72 Right TLE: 75 NO : 102	0	T0= pre-operative T1 = 1 year post-operative T2 = long term post-operative	Range to 2 - 10 years Median follow up TLE patients: 49 months NO patients : 52 months	Verbal memory : 15 words list (German version) Nonverbal memory : Figures learning <u>Normative data + Reliable change index used</u>	Comparison Baseline versus long-term T0 -T2 Left TLE : 60% (lost) versus 15% (gain) in total memory Right TLE: 51% (lost) versus 14% (gain) in total memory Left TLE < Right TLE NO : 50% (lost) versus 12% (gain) in total memory
Engman et al. <i>Prospective study</i>	2006	25 Dominant TLE : 10 Non dominant TLE : 15	25 (no long term follow-up)	T0= pre-operative T1 = 2 years post-operative T2 = long term post-operative	Median follow-up : 9.8	Verbal memory : associative learning Nonverbal memory : Recall Complex figure (Rey) <u>Normative data</u>	Most patients had stable verbal and nonverbal memory postoperatively. Analysis of individual change and group
Anderson-Roswall et al., <i>Prospective study</i>	2010	51 Dominant TLE : 23 Non dominant TLE: 28	23	T0= pre-operative T1 = 2 years post-operative T2 = long term post-operative	Median follow up : 10.9 years	Verbal memory : 10 words list + paired associated words Nonverbal memory : recognition of 30 objects + Recall Complex figure (Rey) <u>Normal controls data</u>	Dominant TLE : Stability in verbal memory Non dominant TLE: Stability in verbal memory
Anderson-Roswall et al., <i>Prospective study</i>	2012	51 Dominant TLE : 23 Non dominant TLE: 28	23	T1 = 2 years post-operative T2 = long term post-operative	Median follow up : 10.9 years	Verbal memory : 10 words list + paired associated words Nonverbal memory : recognition of 30	Analysis of individual change Most patients had stable verbal memory postoperatively.

						objects + Recall Complex figure (Rey) <u>Normal controls data + Reliable change index used</u>	A few dominant TLE patients had a decline at long-term follow-up, but more patients showed partial recovery.
Baxendale et al. <i>Retrospective study</i>	2012	70 Left TLE : 33 Right TLE: 37	0	T0= pre-operative T1 = 3 months post-operative T2 = 1 year post-operative T3 = 10 year post-operative	Range to 5 – 17 years Mean follow-up : 9.1 years	Verbal memory : words list Nonverbal memory : figures learning <u>Normal controls data + Reliable change index used</u>	No changes in verbal memory in 65% of patients but 71% of patients had impair performances preoperatively. No changes in nonverbal memory in 79% of patients but 47% of patients had impair performances preoperatively.
Helmstaedter et al., <i>Retrospective study</i>	2018	369 Left TLE : 84 Right TLE: 77 NO : 208	0	T0= pre-operative T1 = 1 year post-operative T2 = long term post-operative	Range to 5 - 22 years Median follow up : 7 years	Verbal memory : 15 words list (German version) Nonverbal memory : Figures learning <u>Normative data</u>	Comparison baseline versus long-term T0 -T2 Left TLE seizure free : 17% (lost) versus 20% (gain) in verbal memory Left TLE seizure : 37% (lost) versus 4% (gain) in verbal memory Left TLE seizure free : 17% (lost) versus 17% (gain) in nonverbal memory Left TLE seizure : 20% (lost) versus 12% (gain) in nonverbal memory Right TLE seizure free : 10% (lost) versus 16% (gain) in verbal memory Right TLE seizure : 20% (lost) versus 9% (gain) in verbal memory Right TLE seizure free : 7% (lost) versus 13% (gain) in nonverbal memory Right TLE seizure : 17% (lost) versus 13% (gain) in nonverbal memory
Grewe et al., <i>Retrospective study</i>	2019	9 Left TLE : 2 Right TLE : 4 NO : 3	0	T0 = pre-operative T1 = long term post-operative	Range to 16 - 21 years Mean follow up : 18.2 years	Verbal memory : 15 words list + story Nonverbal memory : Figures learning <u>Normative data</u>	Observational results without statistical analysis.

NO: non-operative patients; TLE: temporal lobectomy; WMS: Wechsler memory scale

Table 2. Long-term cognitive outcomes in epilepsy

Authors	Year	Patients	Healthy controls	Design	Follow up duration	Neuropsychological battery	Long term results
Kalska	1991	69 All kind of epilepsy	0		Mean follow-up=10 years	Intellectual efficiency : IQ	Globally, 67% of score's patients did not change, 25% improved and 8% decreased. In memory, 15 to 20% of score's patient decreased. Stable cognitive functioning in individuals with good seizure control.
Holmes et al., <i>Retrospective study</i>	1998	35 All kind of epilepsy	0	T0 = baseline T1 = long term	Follow-up "over 10-year period"	Intellectual efficiency : IQ Verbal memory : story Visual memory : figural learning Language : aphasia screening Executive function : Stroop + TMT + verbal fluency	No differences in the percentage of tests from the entire battery outside normal limits after 10 years. No influence of seizure outcome on cognition.
Thompson et al., <i>Retrospective study</i>	2015	136 Patients with severe intractable epilepsy	0	T0 = baseline T1 = long term	Range 10-27 years Median follow-up=13 years	Intellectual efficiency : IQ + NART Verbal memory : 15 words list Language : naming test + verbal fluency Executive function : TMT + verbal fluency <u>Normative data used</u>	Group analysis reported significant decline on scores for all tests.
Mameniškienė et al., <i>Retrospective study</i>	2016	33 TLE No epilepsy surgery	0	T0 = baseline T1 = long term	Follow up over a period of 13 years ago	Verbal memory : 15 words list + story + paired associated words Nonverbal memory : Recall Complex figure (Rey) <u>Normative data used</u>	Group analysis has reported stability in verbal memory and a decline in nonverbal memory.

IQ=intellectual quotient; TMT=trail making test; NART=national adult reading test; TLE=temporal lobe epilepsy