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Early identification of seizure freedom with medical treatment in patients with mesial temporal lobe epilepsy and hippocampal sclerosis

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Conflict of interest
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Abstract

Background:
Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) is usually associated with a poor response to antiseizure medications. We focused on MTLE-HS patients who were seizure free on medication to: 1) determine the clinical factors associated with seizure freedom and 2) develop a machine-learning classifier to better earlier identify those patients.
Methods:
We performed a retrospective, multicentric study comparing 64 medically-treated seizure-free MTLE-HS patients with 200 surgically-treated drug-resistant MTLE-HS patients. First, we collected medical history and seizure semiology data. Then, we developed a machine-learning classifier based on clinical data.
Results:
Medically-treated seizure-free MTLE-HS patients were seizure-free for at least two years, and for a median time of 7 years at last follow-up. Compared to drug-resistant MTLE-HS patients, they exhibited: an older age at epilepsy onset (22.5 vs 8.0 years, p <0.001), a lesser rate of : febrile seizures (39.0% vs 57.5%, p=0.035), auras (56.7% vs 90.0%, p<0.001), autonomic auras in presence of aura (17.6% vs 59.4%, p<0.001), dystonic posturing of the limbs (9.8% vs 47.0%, p<0.001), gestural (27.4% vs 94.0%, p<0.001), oro-alimentary (32.3% vs 75.5%, p<0.001) or verbal automatisms (12.9% vs 36.0%, p=0.001). The classifier had a positive predictive value of 0.889, a sensitivity of 0.727, a specificity of 0.962, a negative predictive value of 0.893.
Conclusions:
Medically-treated seizure-free MTLE-HS patients exhibit a distinct clinical profile. A classifier built with readily available clinical data can identify them accurately with excellent positive predictive value. This may help to individualize the management of MTLE-HS patients according to their expected pharmacosensitivity.

Keywords: mesial temporal lobe epilepsy, hippocampal sclerosis, seizure freedom, medically-treated, predictive factors, machine-learning

Abbreviations:
MTLE-HS: mesial temporal lobe epilepsy with hippocampal sclerosis
MTLE: mesial temporal lobe epilepsy
TLE: temporal lobe epilepsy
ASM: antiseizure medications
HS: hippocampal sclerosis
FTBS: focal to bilateral tonic-clonic seizures
SEEG: stereo-electroencephalography

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1/Introduction

Patients with mesial temporal lobe epilepsy (MTLE) present different clinical profiles, showing poor or good response to antiseizure medication (ASM).[1-3] Actually, there is no unifying theory to explain the variety of response to ASM, with several potential contributing factors such as disease duration and severity, structural brain lesions, network disturbances with ongoing neural reorganization, and genetic/ metabolic abnormalities.[4,5] Among these factors, etiology of seizures seems to play a critical role.[6,7] Unilateral hippocampal sclerosis (HS), that is the most frequent aetiology of MTLE, is often associated to pharmacoresistance [6] but intriguingly, some MTLE-HS patients may achieve a good seizure control with ASM. Kim et al. report 25% of seizure-free MTLE-HS patients with medical treatment (i.e medically-treated seizure-free patients) in their cohort[1] and Labate et al. found 38.6% of hippocampal sclerosis on brain MRIs of patients with a "mild" form of MTLE.[8] Nevertheless, none of these studies addressed the specificities of medically-treated seizure-free MTLE-HS patients compared to the classical drug-resistant MTLE-HS population.

To gain further insight into the characterization of medically-treated seizure-free MTLE-HS patients and into a better understanding of factors leading to pharmacoresistance in HS, we performed a retrospective multicentric study to determine the clinical factors associated with seizure freedom under medical treatment in MTLE-HS. Our secondary objective was to develop a machine-learning classifier based on clinical data in order to discriminate medically-treated seizure-free patients from drug-resistant patients. The aim was to improve individual patient counselling and determine if presurgical evaluation should be delayed.

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2/ Materials and methods

2.1 Selection criteria of the population and control group

Medically-treated seizure-free MTLE-HS patients were identified from thirteen French tertiary epilepsy centres.

Selection criterion were: 1) adult patients with well-defined MTLE, assessed by experimented epileptologist on medical and EEG data, 2) hippocampal sclerosis on structural brain MRI (characterized by a T1 hippocampal atrophy and a T2 hypersignal, visually assessed by a neuroradiologist, and approved by the epileptologist), 3) MTLE evolving for at least 5 years and 4) seizure freedom under medical treatment (including focal seizures without impaired awareness) for at least 2 years. The clinical and demographic data of these patients were retrospectively reviewed from medical charts.

These selection criterions took into account two possibilities of drug response already described in MTLE-HS patients: 1) a delayed pharmacoresistance during the first years of evolution [9,10] and 2) alternating periods of seizure-freedom and seizure recurrence [3]. We thus chose to include only patients with more than 5 years of evolution and with a long and sustained period of at least 2 years of seizure freedom with ASM (versus 12 months to 2 years in another similar studies).[1,3,11,12]

The control group consisted of 200 patients with unilateral surgically-treated drug-resistant MTLE-HS. These patients were selected from a previously published larger cohort of adult drug-resistant MTLE-HS patients who underwent surgery at the Pitié-Salpêtrière Hospital in Paris between November 1990 and December 2015 (diagnosis of HS confirmed by pathological analysis).[13] Among this cohort of 391 patients, 191 were excluded due to missing data on educational level, medical, and psychiatric history. It should be noted that the control group did not include patients with bilateral hippocampal sclerosis, as this was an exclusion criterion for surgery in this centre.

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Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the local ethics committee of Sorbonne University (CER-2021-089). The patients signed an informed consent form for the use of medical reports and data.

2.2 Recorded variables

Sociodemographic data such as age, sex, level of education, profession, marital status were collected. Education levels were classified by referring to high school graduation (High school graduation or lower, one to 3 years of higher education, more than 3 years of higher education). Medical history included age at the onset of epilepsy, family history of epilepsy, psychiatric comorbidity (mood disorders, anxiety and psychosis), and the occurrence of an initial precipitating injury (meningitis, encephalitis, head trauma, febrile convulsion [both simple and prolonged]). We collected data on the semiology of seizures. We categorized auras according to their semiological description into seven categories: abdominal, experiential, autonomic, psycho-affective, visual, sensory and non specific. For the medically-treated seizure-free group, we also collected the time to achieve seizure freedom, the response to the first ASM, current medication and the number of seizure-free years at the last evaluation. Semiological data for medically-treated seizure-free MTLE-HS patients were collected mainly from medical charts and in 13 cases from video-EEG recordings. Neuropsychological data were not available for the medically-treated seizure free MTLE-HS patients as they did not undergo a presurgical evaluation. We did not collect the standard 20-min EEG data that are not considered as a performant biomarker of seizure control in the literature.[1,14,15]

2.3 Statistical analyses

To compare demographical characteristics between the two groups (medically-treated seizure-free MTLE-HS patients and drug-resistant MTLE-HS patients), Wilcoxon-Mann-Whitney test

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was performed for numerical variables and Fisher's exact test for categorical variables. Pvalues were corrected for multiple comparisons using the Benjamini-Hochberg method. Statistical significance was defined as $p < .05$.

In a second step, we developed a classifier that aimed to discriminate between medically-treated seizure-free and drug-resistant MTLE-HS patients based on demographics, medical history, and semiological data (List of data included in the model detailed in the **Supplementary Materials**). Our objective was to better identify MTLE-HS patients with a greater chance of response to ASM. Therefore, we minimized the risk of error when categorizing a patient as "Seizure-free" by selecting a positive predictive value higher than 0.9, to reduce the probability of inappropriately delay referral to pre-surgical assessment in patient misclassified as "seizure-free". With respect to the group balance, dataset was split in a 80%-set used to find the best algorithm, which was then applied on the testing set (20%), i.e. on patients independent from the classifier construction, in order to evaluate its performances. The process to select the best algorithm using repeated 3-fold cross-validation is detailed in the **Supplementary Materials.**

Statistical analyses were performed using R 4.1.2. (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.) and with packages randomForest version 4.7-1 ; e1071 version 1.7-9; and xgboost version 1.5.2.1.

Data Availability

The anonymized data that support the findings of this study are available on request from the corresponding author. The web-application of the algorithm is available at https://github.com/mhouot/MTLE-HS_algorithm .

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3/ Results

3.1 Comparisons between medically-treated seizure-free and drug-resistant MTLE-HS patients

The proportion of missing data in the overall database was 11.8% in both groups (mostly employment and marital status data). Sixty-four medically-treated seizure-free MTLE-HS patients from 13 French tertiary epilepsy centres and 200 drug-resistant MTLE-HS patients were included. Comparisons between medically-treated seizure-free and drug-resistant MTLE-HS patients are shown in Table 1.

Social and demographic data

The two groups were not different in terms of sex-ratio, employment, or marital status.

The only significant statistical differences concerned the education level. 59.6% of medically-treated seizure-free MTLE-HS patients stopped their studies before obtaining a high-school degree, while only 39.0% of drug-resistant MTLE-HS patients did. But when focusing on those who performed high-school education, only 0.5% of drug-resistant MTLE-HS patients achieved at least 3 years of higher education, while 11.5% of medically-treated seizure-free MTLE-HS patients did.

Medical history

Medically-treated seizure-free MTLE-HS patients were seizure-free for a median time of 7 years [5;11] at last evaluation. 34.5% of medically-treated seizure-free MTLE-HS patients were seizure free after the first ASM trial. The most frequently used ASM in the seizure-free group were levetiracetam (26.1%), lamotrigine (19.6%), valproic acid (9.8%), carbamazepine (8.7%) and lacosamide (8.7%) (Respective proportions of the other ASM are shown in **Supplementary Materials**). These patients had tried a median of 2 [2;3] treatments before achieving seizure-freedom. Regarding the findings on interictal EEG recording, 3.1% of the patients had bilateral anomalies, 54.7% had anomalies homolateral to the HS and 42.2% had no anomalies.

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The two groups did not exhibit significant differences in terms of early events history such as prematurity, meningitis/encephalitis or head trauma, or in terms of psychiatric history. There was a trend for more frequent familial history of epilepsy in the drug-resistant MTLE-HS group (23.6% vs 10.0%, p=0.062).

Two significant differences were noted: 1) the frequency of childhood febrile seizures was significantly lower in medically-treated seizure-free MTLE-HS patients (39.0% vs 57.5%, p=0.035) and 2) medically-treated seizure-free MTLE-HS patients were significantly older at the onset of epilepsy (22.5 [13.0;41.5] vs 8.0 [4.0;14.0], p<0.001).

In addition, there was a lower proportion of ASM polytherapy in the medically-treated seizure-free group (number of ASM at inclusion, 1.0 [1.0; 2.0] vs 2.00 [2.0; 3.0], p<0.001).

Seizure semiology

Video EEG recording of seizure was available for only 13 (20.3%) medically-treated seizure-free MTLE-HS patients, and for all drug-resistant patients.

The occurrence of auras was significantly lower in the medically-treated seizure-free group (56.7% vs 90.0%, p<0.001). Among MTLE-HS patients who exhibited auras, medically-treated seizure-free MTLE-HS patients were less likely to have an autonomic aura (17.6% vs 59.4%, p<0.001) whereas no differences were noted regarding the other auras subtypes. Regarding focal seizures with impaired awareness, medically-treated seizure-free MTLE-HS patients had less gestural (27.4% vs 94.0%, p<0.001), oro-alimentary (32.3% vs 75.5%, p<0.001) or verbal automatisms (12.9% vs 36.0%, p=0.001). They also showed less dystonic posturing of the limbs (9.8% vs 47.0%, p <0.001).

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3.2 Prediction of seizure-free status with medical treatment in MTLE-HS patients

The best performances were obtained with support-vector machine (SVM) method. The median [95%CI] positive predictive value was 0.903 [0.783;0.963], with a median sensitivity of 0.743 [0.629;0.8], a median specificity of 0.972 [0.936;0.991] and a median negative predictive value of 0.921 [0.891;0.938]. Those results were confirmed by the performances evaluated on the testing set with a positive predictive value of 0.889, a sensitivity of 0.727, a specificity of 0.962, a negative predictive value of 0.893. The classifier is available at https://github.com/mhouot/MTLE-HS_algorithm (open-source). Tutorial available in **Supplementary Materials**.

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4/ Discussion

In this multicentric retrospective study, we present a substantial cohort of MTLE-HS patients who have achieved long term seizure freedom with ASM. We showed that medically-treated seizure-free MTLE-HS patients differed from the classically described population of drug-resistant MTLE-HS patients in terms of medical history and seizure semiology. Using a machine-learning approach, we were able to develop a reliable classifier to identify MTLE-HS patients with a good response to ASM. The distinctive clinical features that we used for this machine-learning approach are easily assessable by a non-expert physician and do not require the facilities of an expert centre. This algorithm could be an easily accessible and manageable tool to counsel adequately MTLE-HS patients during the first consultation and delay the referral to a pre-surgical evaluation if a good response to ASM could be predicted.

Distinctive features between medically-treated seizure free and drug-resistant MTLE-HS patients

While the presence of hippocampal sclerosis is strongly associated with drug resistance[6], the first data published in 1999 by Kim et al.[1] reported a 25% rate of seizure-freedom with medication in a MTLE-HS cohort. Studies that have looked specifically at medically-treated seizure-free patients with hippocampal sclerosis are rare (26 cases found in the literature).[1] Most studies of MTLE with a good prognosis named "mild" or "benign" MTLE include both lesioned (including HS) and non-lesioned patients,[2,3,8,14,16-21] some of whom still having rare seizures that are not considered disabling, making comparisons with studies in the literature complex. To our knowledge, our medically-treated seizure-free MTLE-HS highly selected cohort is the largest one published to date.

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Demographic and anamnestic data

Our results concerning educational background show that the distribution of educational levels is different between the two populations. In an intriguing way, there was a higher proportion of medically-treated seizure-free MTLE-HS patients who stopped their studies before obtaining a high-school degree. But logically, patients from both groups who stopped within the first three years their high school education had an earlier onset of epilepsy than those who did more than 3 years of higher education and a higher proportion of medically seizure-free MTLE-HS patients achieved at least 3 years of higher education. This outlines the impact of age at onset of epilepsy on patients' education as already demonstrated by Asadi-Pooya et al. [22] In contrast to previous studies, [22-24] we found no difference between the two groups in terms of employment rate, probably due to the relatively high employment rate in both groups, nor in psychiatric history.

Interestingly, we found a tendency to have less family history of epilepsy in the medically-treated seizure-free group. Inconsistent results have been reported in the literature. Some teams found that patients with "mild" TLE are closely associated with familial forms of TLE or that MTLE patients with familial history of epilepsy had a better prognosis,[2,18,25] findings supported by the existence of hippocampal sclerosis on MRI of asymptomatic relatives of patients with a familial form of MTLE.[26] At the opposite, as in our study, other studies have reported similar[17] or lower proportions[1] of family history of epilepsy in well-controlled MTLE patients.

Two major significant differences were noted here: 1) the frequency of childhood febrile seizures was significantly lower in medically-treated seizure-free MTLE-HS patients and 2) medically-treated seizure-free MTLE-HS patients were significantly older at the onset of epilepsy.

A lower incidence of childhood febrile seizures in well-controlled MTLE patients was already described by Aguglia.[14,18] In these studies, the proportion of patients with febrile seizures was

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lower than in our study (11% versus 38.9%), related to the fact that they included patients with and without hippocampal sclerosis. Usually, hippocampal sclerosis as in our drug-resistant group, is highly associated with a history of febrile seizures.[27,28] As in our study, most studies found that patients with good seizure control are older at the onset of epilepsy.[1,2,11,14,18,23,24] A late age at onset of epilepsy has been identified as a positive prognostic factor in all forms of epilepsy[24] including MTLE with or without HS.[14] At the opposite, MTLE patients with hippocampal sclerosis have usually an earlier onset than other MTLE patients.[27]

Clinical data

Medically-treated seizure-free MTLE-HS patients differed from drug-resistant MTLE-HS patients by a lower proportion of 1) auras, 2) autonomic auras in presence of aura, 3) gestural, oro-alimentary or verbal automatisms and 4) dystonia of the limbs. There are many arguments that MTLE-HS is a network disease rather than one centered on a single lesion.

The distinct clinical symptomatology in medically-treated seizure-free MTLE-HS can certainly be explained by differential spreading networks from an identical focus: the sclerotic hippocampus. In MTLE with HS, studies indicate that the amygdala and hippocampus are the hub regions and that secondary activation occurs preferentially to insular and medial frontal regions [29] or to the basal ganglia.[30] Interestingly, our data suggest that in medically-treated seizure-free MTLE-HS patients, secondary propagation could not occur preferentially in these regions. Signs that are supposed to result mainly from: i) an insulo-opercular cortex involvement, i.e autonomic aura and oroalimentary automatisms, ii) a frontal involvement, i.e gestural or verbal automatisms or iii) a basal ganglia involvement, i.e dystonic posturing of the limbs, are less frequent in the medically-treated seizure-free MTLE-HS patients subgroup. Indeed, autonomic symptomatology is supposed to be produced by activation of the insular cortex, anterior cingulum, or supplementary sensorimotor area, all areas that have been found to share the same subcortical relay station as the hypothalamus.[31-33] Similarly, stereo-EEG

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(SEEG) data have indicated that the occurrence of oro-alimentary automatisms in seizures originating in anterior and medial temporal lobe depended on their propagation to insulo-opercular areas, especially to their anterior part.[34-36] SEEG exploration have also shown that, in MTLE, gestural automatisms only occurred when the discharges spread to extratemporal cerebral structures, especially the opercular and cingular cortices.[34,36-38] Brain mechanisms underlying dystonic posturing obviously reflect a specific primary spread of the ictal discharge to the basal ganglia.[30] Imaging studies suggest that ictal dystonic posturing was significantly associated to an increase in perfusion or a decrease in metabolism of the basal ganglia contralateral to the dystonic limb.[39,40]

The hypothesis is that connection patterns in a given pathology, i.e MTLE-HS, are malleable and may reflect individual plastic changes that have occurred in the course of a patient's lifetime, both in response to physiological events and to seizures. These distinct epileptogenic networks could partly explain the existence or absence of pharmacoresistance.[41] In line to this hypothesis, Fang et al.[42] recently proposed the neural network hypothesis, which states that seizure-induced degeneration and remodeling of the neural network suppress the endogenous antiseizure system and lead to ASM failure. An association between the presence of auras and automatisms and the drug-resistant status of MTLE patients has also been addressed by Stefanatou et al. who examined 83 consecutive MTLE patients (with (n=28) and without HS).[16] As in our study, they found a lower frequency of auras and automatisms in drug responsive MTLE patients.

These results are not in accordance with those of Agulia et al.[2,14,18] who described a higher frequency of autonomic, experiential and abdominal symptoms in "mild" MTLE as compared to drug-resistant MTLE. The explanation may again come from the non-homogeneous population of MTLE patients of these studies.

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Finally, the proportion of focal to bilateral tonic-clonic seizures (FTBS) was higher in both groups (medically-treated seizure-free MTLE-HS: 66.1% vs drug-resistant MTLE-HS: 71.9%), than previously reported in literature.[36] This can be explained by the fact that we took into account here the existence of at least one FTBS during the evolution of the epilepsy and not their frequency, a parameter difficult to estimate from a retrospective study. Similarly, Bone et al.[43] have shown an association between the presence of HS and a higher frequency of FTBS (80% in MTLE-HS versus 67% in other TLE patients), and a high rate of FTBS was also found in Aguglia's study (58 to 63.3%).[14]

Prediction of seizure outcome with medical treatment in MTLE-HS patients

As a result, we were able to develop a reliable and accurate classifier. Another team had tried to develop an algorithm to predict the ASM response in MTLE[19] but its diagnostic performances were significantly lower than those of our classifier. Our classifier is simple to use as the variables included are easy to collect for the clinician. It has a good diagnostic performance, including a very high positive predictive value. The objective is twofold for newly diagnosed MTLE patients with hippocampal sclerosis: 1) to provide them with appropriate advice covering their future life and 2) to delay or avoid the referral to a presurgical assessment. It is clear that life choices, especially professional ones, are very much influenced by the drug-sensitivity of the epilepsy. In MTLE-HS patients, the usual pharmacoresistance encourage practitioners to address the issue of a presurgical assessment at a very early stage. Our classifier could help to identify the few patients who have a high chance to achieve seizure-freedom with ASM and do not require early referral to presurgical evaluation. The classifier needs to be tested on a larger population and in a prospective approach.

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Limitations and strength of the study

Our analyses were retrospective, based on medical and seizure charts and we acknowledge the limitations of a retrospective study: 1) the collection of objective signs such as automatisms or dystonia may have been biased in the medically-treated seizure-free group since only 20% were objectively assessed by video-EEG recordings, and 2) we were unable to establish the time to drug resistance in the drug-resistant group.

Another limitation of our study is its limited recruitment to tertiary centres, which may have lowered the number of included patients, as seizure-free patients are less often referred to these centres.

The strengths of our study are the inclusion of well-characterized medically-treated seizure-free MTLE-HS patients with stringent and well-defined inclusion criterion. Indeed, our patients had been seizure-free for a median of 7 years, which can be considered as long-term seizure-freedom. We also decided to include only strictly seizure-free MTLE-HS patients in opposition to previous studies,[2,8,17,18,20,21] where patients gathered as "mild", "benign" or "drug-responsive" TLE formed a heterogeneous group that ranged from complete seizure freedom to less to three seizures per year (focal with impaired awareness or focal to bilateral tonic-clonic). It would be interesting to perform afterwards a dedicated MRI study of hippocampal volumetry and connectivity to assess if there are distinctive patterns between these two populations and thus define if these patients suffer from a different form of epilepsy than the drug-resistant MTLE-HS patients.

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5/ Conclusions

Our multicentric study presents data from the larger cohort of medically-treated seizure-free MTLE-HS, population that has been overlooked in the literature. We have shown that these patients present atypical clinical features compared to the commonly described drug-resistant MTLE-HS population: absence of childhood febrile seizures, later age at onset of epilepsy, absence of auras, lack of ictal dystonic posturing or automatisms. These features constitute "green flags" that can enable to hope for a sustained seizure-freedom with ASM. Combined in an efficient predictive model with other easily accessible anamnestic data, these "green flags" may help in a very early stage to reliably identify medically-treated seizure free MTLE-HS from drug-resistant MTLE-HS patients in order to improve patient counselling and the referral to an early pre-surgical evaluation. These findings will need validation from larger prospective studies.

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Statements

Conflict of interest
None of the authors has any conflict of interest to disclose.

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Ethical Publication Statement
-We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.
-We used the STROBE reporting guidelines.
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-IRB Statement:
The study was approved by the local ethics committee of Sorbonne University (n° CER-2021-089). The patients signed an informed consent form for the use of medical reports and data.

Authors contributions
M.C and S.D had the idea for the study, included patients and wrote the initial protocol and analysis plan. M.C collected the data. M.C, M.H and S.D did the data analysis. M.H did the statistical analysis and developed the machine-learning classifier. M.C. produced the table and wrote the first draft of the manuscript. M.H and S.D further reviewed the manuscript and contributed to the final version of the manuscript. All other authors (N.C, W.S, C.M, H.C, L.V, M.G, B.H, A.B, S.L, L.Maz, L.Min, L.Mai) included in the study patients from their epilepsy centres and contributed to editing and commenting on the final version.

Data availability statement
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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6/ References

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Figures legends

Table 1: Comparisons between medically-treated seizure-free and drug-resistant MTLE-HS patients

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	Medically-treated seizure-free MTLE-HS N=64 (24.24%)	Drug-resistant MTLE-HS N=200 (75.76%)	*p‡*	*Corrected p⌋*
Demographics				
Sex (women)	33 (51.56%)	111 (55.50%)	*0.666*	*0.719*
Education (y)			*<0.001**	*<0.001**
≤12	31 (59.62%)	78 (39.00%)		
13-15	15 (28.85%)	121 (60.50%)		
>15	6 (11.54%)	1 (0.50%)		
Employed	47 (85.45%)	150 (79.79%)	*0.435*	*0.534*
In a relationship	33 (66.00%)	65 (51.18%)	*0.093*	*0.162*
Medical History				
Prematurity	2 (3.64%)	8 (5.23%)	*1.000*	*1.000*
Family history of epilepsy	6 (10.00%)	34 (23.61%)	*0.032**	*0.062*
Psychiatric history	13 (21.67%)	51 (31.88%)	*0.182*	*0.257*
Febrile convulsion	23 (39.00%)	115 (57.50%)	*0.017**	*0.035**
Head trauma	9 (16.36%)	29 (14.50%)	*0.831*	*0.863*
Meningitis or encephalitis	10 (16.13%)	17 (8.50%)	*0.096*	*0.162*
Clinical characteristics				
Age at the onset of epilepsy (y)	22.50 [13.00, 41.50]	8.00 [4.00, 14.00]	*<0.001**	*<0.001**
Age at surgery (y)		34.00 [28.00, 43.00]		
Age at seizure freedom (y)	46.00 [35.00, 55.00]			
Time from onset to surgery (y)		24.00 [17.75, 33.00]		
Disease duration (y)	19.50 [11.75, 37.00]	47.00 [38.75, 54.00]	*<0.001**	*<0.001**
Duration of seizure-freedom (y)	7 [5;11]			
HS side on MRI			*0.014**	*0.031**
Bilateral	3 (4.84%)	NA		
Right	26 (41.94%)	100 (50.00%)		
Left	33 (53.23%)	100 (50.00%)		
1st ASM efficacy (yes)	20 (34.48%)			
Nb of ASM tried before seizure freedom	2 [2, 3]			
ASMs number §	1.00 [1.00, 2.00]	2.00 [2.00, 3.00]	*<0.001**	*<0.001**
Semiology of seizure				
Presence of aura	34 (56.67%)	180 (90.00%)	*<0.001**	*<0.001**
Abdominal aura ¥	16 (47.06%)	104 (57.78%)	*0.264*	*0.923*
Psycho-affective aura ¥	12 (35.29%)	59 (32.78%)	*0.843*	*1.000*
Autonomic aura ¥	6 (17.65%)	107 (59.44%)	*<0.001**	*<0.001**
Experiential aura ¥	9 (26.47%)	47 (26.11%)	*1.000*	*1.000*
Visual aura ¥	5 (14.71%)	23 (12.78%)	*0.782*	*1.000*

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Sensory aura ¥	3 (8.82%)	20 (11.11%)	*1.000*	*1.000*
Non specific aura ¥	4 (11.76%)	21 (11.67%)	*1.000*	*1.000*
Gestural automatisms	17 (27.42%)	188 (94.00%)	*<0.001**	*<0.001**
Oro-alimentary automatisms	20 (32.26%)	151 (75.50%)	*<0.001**	*<0.001**
Verbal automatisms	8 (12.90%)	72 (36.00%)	*<0.001**	*0.001**
Dystonia of a limb	6 (9.84%)	94 (47.00%)	*<0.001**	*<0.001**
At least one focal to bilateral tonic-clonic seizure	41 (66.13%)	143 (71.86%)	*0.426*	*0.534*

Notes. Data are given as median [first quartile, third quartile] for continuous variables and as count (percentages) for categorical variables.

¥ Percentages of specific aura were calculated on patients who experienced aura.

‡ Wilcoxon-Mann-Whitney test was used to compare groups for numerical variables and Fisher's exact test for categorical variables.

∫ pvalues correctd for multiple testing using Benjamini-Hochberg method.

§ at evaluation for Medically-treated seizure-free *group, at surgery for Drug-resistant*

Abbreviations: MTLE-HS = medial temporal lobe epilepsy with hippocampal sclerosis, ASM = antiseizure medication, SF = seizure-free, PR = drug-resistant, y = years, HS =hippocampal sclerosis

MRI= magnetic resonance imaging

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Supplementary materials

-Features tested for the classifier development

Twenty features were tested for the classifier development:

- **Demographics**: sex
- **Clinical data**: age at onset
- **Medical history**: prematurity; family history of epilepsy; febrile convulsion; head trauma; meningitis or encephalitis
- **Seizure semiology**: presence of aura; presence of abdominal aura; presence of psychoaffective aura; presence of autonomic aura ; presence of experiential aura ; presence of visual aura ; presence of sensory aura ; presence of non specific aura ; presence of gestural automatisms ; presence of oroalimentary automatisms ; presence of verbal automatisms ; dystonia of a limb ; occurrence of at least one focal to bilateral tonic-clonic seizure

- Process to select the best algorithm

Performances were estimated using 500 samples of 3-fold cross-validation, leading to estimate median indicators and their 95% credibility intervals. Indeed, for each bootstrap sample, predicted probabilities of the validation set (as an independent cohort) (i.e. 1/3 of the sample size) were obtained using the algorithm fitted on the training set (i.e. 2/3 of the sample size). The threshold of fitted probabilities on the training set, obtained by maximizing the Youden index among those with positive predictive value higher than 0.9, was then used to classify subjects of the validation test as true positive, false positive, true negative, or false negative. One at a time, each of the 3 sets became the validation set and at the end, all subjects were classified leading to calculate the performance indicators of the bootstrap sample: Youden index, sensitivity, specificity, positive predictive value, and negative predictive value. Median and 95% credibility intervals were calculated for each performance indicator on the indicator distribution estimated by bootstrap. Tested machine learning algorithms were logistic regression, random forests, SVM (support-vector machine) and XGBoost (eXtreme Gradient

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Boosting). Each machine learning technique was fitted several times with different combination of parameters : for regression logistic, no parameter needed to be fixed ; for random forests (RF), 8 combinations were tested (mtry ∈ {2;√p}, ntree ∈ {500;1000}, maxnodes ∈ {4;10}) ; for support vector machine (SVM), 9 combinations were tested (gamma ∈ {0.01;1;10}, cost ∈ {0.01;1;10}) ; for eXtreme Gradient Boosting (XGBoost), 8 combinations were tested (eta ∈ {0.1;0.3}, gamma ∈ {0;0.5}, max.depth ∈ {3;6}). Parameters names were those from R packages.

The best algorithm was defined as the one that maximized the median Youden index among those with a median positive predictive value greater than 0.9. Performance indicators of testing set was calculated using the best algorithm trained on the 80%-set.

-Tutorial: How to download and run our classifier?

-Get to https://github.com/mhouot/MTLE-HS_algorithm

- You can download the all data and classifier or just run the app to test a patient.
- Testing a patient without R download on: https://mhouot.shinyapps.io/mtle-hs_algorithm/

-To get the algorithm on your computer:

-Download the free software R and R studio and install it on your computer from https://cran.r-project.org .

-Then, you need to install the shiny package in R: Copy and paste in the R console

```
if (!require('shiny')) install.packages("shiny")
```

-To run the application, you have to load the library and use the function runGitHub(). Copy and paste in the R console:

```
library(shiny)
shiny::runGitHub("MTLE-HS_algorithm", "mhouot")
```

-Choose between the two tabs:

1. *Select one patient's data*: to obtain the probability of being medically seizure-free by entering patient data one by one
2. *Upload a file (.xlsx) of the data patients*: to obtain the probability of being medically seizure-free of several patient at a time. See the data_test.xlsx file in the datas folder for example.

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QR code for the shiny app



-Table 2: Antiseizure medication in the medically-treated seizure-free MTLE-HS group

	Nb in the medically-treated seizure-free MTLE-HS group (Total number of ASM data collected = 92) §
Anti-seizure medication	
Levetiracetam	24 (26.1%)
Lamotrigine	18 (19.6%)
Valproic acid	9 (9.8%)
Carbamazépine	8 (8.7%)
Lacosamide	8 (8.7%)
Eslicarbazépine	5 (5.4%)
Oxcarbazépine	5 (5.4%)
Perampanel	4 (4.3%)
Phénobarbital	4 (4.3%)
Prégabaline	4 (4.3%)
Clobazam	1 (1.1%)
Gabapentine	1(1.1%)
Zonisamide	1(1.1%)

Notes: Data are given as count and percentages for categorical variables.

§ Some patients were under several ASM (1 to 3 ASM).

Abbreviations: Nb = number, ASM = antiseizure medication, MTLE-HS = mesial temporal lobe epilepsy with hippocampal sclerosis

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