Epilepsia
Official Journal of the International League Against Epilepsy

The phenotype of bilateral hippocampal sclerosis and its management in 'real life' clinical settings

Journal:	*Epilepsia*
Manuscript ID	Draft
Manuscript Type:	Full length original research paper
Date Submitted by the Author:	n/a
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Key Words:	Bilateral hippocampal sclerosis, Epilepsy surgery, Phenotype, Seizure semiology, EPIGEN

The phenotype of bilateral hippocampal sclerosis and its management in 'real life' clinical settings

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Running title: The phenotype of bilateral HS (29 characters)

Key words: Bilateral hippocampal sclerosis, epilepsy surgery, phenotype, seizure semiology

Number of text pages: 17 (main text)

Number of words (summary): 299

Number of words (main text): 4476

Number of tables (main and supplementary): 3 main and 2 supplementary

Number of figures (main and supplementary, and how many are in color): 4 main and 2 supplementary, all colour

Supporting figures and tables are included

Author Disclosures:

The authors declare no conflicts of interest

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Abstract:

Objective:

There is little detailed phenotypic characterisation of bilateral hippocampal sclerosis (HS). We therefore conducted a multicentre review of all people with pharmacoresistant epilepsy and bilateral HS to better determine their clinical characteristics.

Methods:

Databases from 11 EPIGEN centres were searched. For identified cases, clinicians reviewed the medical notes, imaging, EEG, video-EEG and neuropsychometric data. Data were irretrievably anonymised and a single database populated to capture all phenotypic information. **These data were compared with phenotyped cases of unilateral HS from the same centres**

Results:

In total, 96 patients with pharmacoresistant epilepsy and bilateral HS were identified (43 female, 53 male; age range 8-80 years). 25% had experienced febrile convulsions and 27% patients had experienced status epilepticus. The mean number of previously tried anti-epileptic drugs was 5.3 and the average number of currently prescribed medications was 2.9. There was a high incidence of cognitive and psychological difficulties. The majority of patients continued with long-term medical therapy alone. Sixteen patients proceeded to, or were awaiting, neurostimulation and eleven underwent surgical resection. One patient was rendered seizure-free post-resection, and there was an improvement in seizures for three other cases.

By comparison, of 201 patients with unilateral HS, a significantly higher number (44.3%) had febrile convulsions and a much lower percentage had experienced status epilepticus (11.4%). Importantly, focal aware seizures were common in patients with unilateral HS occurring in 41.8% (84/201) while such seizures were less frequently observed in people with bilateral HS, and were never observed exclusively ($p=0.002$; Fisher's exact test)

Significance:

The current work describes the phenotypic spectrum of people with pharmacoresistant epilepsy and bilateral HS, **highlights salient clinical differences from patients with unilateral HS and** provides a large platform from which to develop further studies, both epidemiological and genomic, to better understand etiopathogeneisis and optimal treatment regimes in this condition.

Key words: Bilateral hippocampal sclerosis, epilepsy surgery, phenotype, seizure semiology

Key points:

1. Bilateral HS is a **relatively** rare, but important, cause of pharmacoresistant epilepsy
2. 25% of people with bilateral HS experienced a febrile seizure and no patient had focal aware seizures alone compared to 44.3% of people with unilateral HS having had a febrile seizure and 41.3% of unilateral HS cases having focal aware seizures
3. 27% of patients with bilateral HS had experienced status epilepticus, not necessarily at the onset of seizures
4. Patients with bilateral HS had often tried many anti-epileptic medications and had high rates of cognitive and psychiatric co-morbidity
5. In this multicentre study, only a minority of patients with bilateral HS proceeded to surgical (palliative) resection of one hippocampus

The phenotype of bilateral hippocampal sclerosis and its management in 'real life' clinical settings

Introduction:

The most common identifiable cause of pharmacoresistant focal epilepsy in adults is hippocampal sclerosis (HS). In the majority, HS is unilateral and in these cases surgical resection of the affected hippocampus can associate with seizure freedom in up to 70% of cases [1,2]. However, why HS seems to be predominantly unilateral has remained uncertain.

It has been long appreciated that there are cases of drug-resistant focal epilepsy in whom HS is bilateral. For example, in 1958 Wilder Penfield identified two cases who developed profound memory difficulties following standard left temporal lobectomy. He hypothesised that these two patients had significant, but unsuspected, right hippocampal pathology such that when he resected the left hippocampus, the effect was similar to bilateral temporal lobectomy[3]. Penfield's theory was substantiated many years later when one of his cases (patient PB) was analysed at autopsy and was found to have right sided hippocampal atrophy[4]. Penfield's noble publication in which he illustrated unforeseen complications of his resective surgery, led Scoville to contact him and highlight the case of Henri Molaison (Patient HM) who had undergone bilateral temporal lobectomies and subsequently developed dense anterograde amnesia. Milner travelled to Connecticut to study HM and it quickly became evident that bilateral temporal lobectomy was contraindicated owing to the profound cognitive sequelae[5,6].

Such observations, now six decades old, draw attention to the fact that bilateral hippocampal pathology can pose many difficulties. The development of MRI has enabled much better detection of bilateral HS[7], a condition in which seizures are perceived to be very drug resistant and surgical options seem potentially limited. **The exact incidence of bilateral HS is unknown** and there is little work specifically examining the phenotypic characteristics of a large cohort of patients with bilateral

HS with, in particular, minimal description of patients with bilateral HS who do not proceed to surgical treatment. To address this, we collated data across an international consortium of tertiary epilepsy centres (EPIGEN) to evaluate the characteristics of such patients as well as surveying management of patients with bilateral HS in a 'real-world' setting. **In addition we compared our data from bilateral HS cases to a large collection of unilateral HS patients collated from the same centres.**

Methods:

EPIGEN is an international consortium of tertiary referral epilepsy centres which aims to deliver clinically facing genomic research. All full member institutions of the EPIGEN consortium (Columbia University Medical Center and New York University Langone Medical Center, New York, USA; Beaumont Hospital, Royal College of Surgeons of Ireland, Dublin, Ireland; Duke University, Durham, USA; The Royal Melbourne Hospital, Melbourne, Australia; The Chinese University of Hong Kong, Hong Kong; Cork University Hospital, Cork, Ireland; Toronto Western Hospital, Ontario, Canada; Swansea University Medical School, UK; Hôpital Erasme – ULB, Bruxelles, Belgium; John Radcliffe Hospital, University of Oxford, UK), searched clinically held databases for patients with bilateral HS. Inclusion criteria were kept deliberately broad (Supporting Table 1), with the principal criterion being that patients had to have evidence of bilateral mesial temporal sclerosis on an epilepsy protocol brain MRI, as determined by a neuroradiologist and/or epileptologist. Bilateral HS was defined as demonstration of significant atrophy of both hippocampi with or without increase in signal of one or both hippocampi. Male and female patients of any age were included as were patients with dual pathology detected on brain imaging. We also specified that patients had to have tried two or more appropriate anti-epileptic drugs (AEDs) to enable study of patients with bilateral HS and pharmacoresistant epilepsy.

Researchers at each EPIGEN Centre then performed detailed phenotypic analysis on each identified patient, through thorough review of medical notes/clinical databases including imaging reports, electroencephalogram (EEG) recordings and video-EEG data, neuropsychometric assessments, operation notes, histology reports and clinical outcomes. Data were entered based on the medical information held at the EPIGEN centre. Data on patients who were no longer under the care of an EPIGEN centre were collected to the point at which medical documentation at the EPIGEN centre ceased.

Phenotypic data were de-identified and entered into a database with 25 principal entry fields (See Supporting Table 2). Researchers were encouraged to leave fields blank if there was any uncertainty following review. All data were then pooled and two of the authors (AS and PD) analyzed the data. Where any disagreements in data interpretation were identified, consensus was agreed through careful discussion. All data were then subject to qualitative evaluation and relevant quantitative analyses were performed.

We further compared the data obtained from the cohort of people with bilateral HS to 201 patients with unilateral HS collated from the same EPIGEN centres enabling statistical comparison of phenotypic characteristics between people with bilateral HS and unilateral HS.

Results:

Basic phenotypic data

Nine centers identified patients from patient databases with sizes ranging from 116 to 5000. Two centers identified patients from their clinics, which see an average of 1500-2000 patients per year. In total, 96 patients with bilateral HS who fulfilled the inclusion criteria were identified across the centres (43 female, 53 male). The ethnic diversity of patients captured reflects the centres that contribute to EPIGEN. The majority of cases were Caucasian (72/96), 9 of Asian descent (3 Indian, 4

Chinese, 2 not further specified) and 4 of African heritage. Racial origin was not documented formally in 11 cases.

The duration of follow-up at the EPIGEN centres ranged from 4 weeks to 58 years (mean 7.5 years). The age at time of data capture ranged from 8 to 80 years (mean 49.2 years; SEM 1.64) and age of seizure onset ranged from 0.5 to 63 years (mean 17.4 years; SEM 1.51 years). The average documented duration of seizures was 30.4 years, with a range of 1-79 years (SEM 1.82 years).

Etiopathogenesis of epilepsy

Of the 96 patients studied, 14 (14.5%) had a confirmed family history of epilepsy. However, in only 4 (4.2%) patients was epilepsy identified in first-degree relatives and in two of these cases the epilepsy identified in family members was acquired (post-traumatic epilepsy, brain tumor).

The majority of patients did not have a documented history of febrile seizures (63 patients had no evidence of febrile seizures; 9 not documented). In the 24 (25.0%) patients who did have febrile seizures, two had prolonged febrile seizures. Interestingly, 5 patients who had febrile seizures had a positive family history of epilepsy, although in one case the affected relative had an acquired cause for their epilepsy. Similarly, 4 patients who had febrile seizures had additional clearly defined etiologies for developing epilepsy (1 meningitis in childhood, 2 meningoencephalitis in adulthood and 1 had neurosurgery in childhood (burr holes) owing to presumed intracranial hemorrhage).

We determined the likely etiology of the patient's HS through comprehensive assessment of each individual case. In 61 (63.5%) patients, no cause was identified. The most common identifiable cause for bilateral HS was infection, principally meningoenecephalitis (Figure 1). Four patients developed epilepsy secondary to birth trauma and 4 after traumatic brain injury outside of the neonatal period. **Similarly, four patients developed bilateral HS following new onset refractory status epilepticus (NORSE).** Three patients were found to have a potentially causal auto-antibody (one voltage gated potassium channel (VGKC) antibody, one anti-glutamic acid decarboxylase (GAD) antibody and one

not further specified, and were therefore classified as autoimmune epilepsy. **However, the proportion of cases tested for autoantibodies was low at 12 out of 94 cases (no data available for 2 patients). This likely reflects that the cases were acquired over many decades and many patients would have had a diagnosis of bilateral HS made long before antibody-mediated epilepsy was recognised or specific antibody testing available.**

Seizure type

In averaging all cases where a seizure frequency per month was recorded or could be derived (e.g. investigator recorded seizure frequency per week), the mean seizure frequency was 10.9 seizures per month. Seizure type was analysed in detail (Supporting Figure 2). The majority of patients had either focal seizures with impaired awareness and focal to bilateral tonic clonic seizures (44/96; 45.8%). Focal impaired awareness seizures alone occurred in 23/96 (23.9%) and focal seizures with and without impairment of awareness and focal to bilateral tonic clonic seizures in 16/96 (16.7%). No patient had only focal aware seizures. Four patients were reported to have bilateral tonic clonic seizures alone. Most patients did not experience status epilepticus either at outset or at any point (64/96; 66.7%). In total 26 (27.1%) patients had a previous history of status epilepticus and in 6 cases information regarding episodes of status epilepticus was not recorded.

Medication history

Patients included in this cohort had pharmacoresistant epilepsy and many patients had tried multiple AEDs. Only 7 cases did not have full datasets available for previously trialled medication and data were complete for currently prescribed treatments. The range of number of AEDs previously tried was 1-15, with a mean number of previously tried AEDs being 5.32. The average number of currently prescribed AEDs was 2.99 (range 1-6).

The AEDs trialled previously are illustrated in Figure 2A. The most commonly tried AED was carbamazepine followed by, in descending order, valproate, lamotrigine, phenytoin and

levetiracetam. By contrast, levetiracetam was the most commonly prescribed current AED followed by, again in descending order, lamotrigine, clobazam, valproate and carbamazepine (Figure 2B). A wide range of other second and third line AEDs were also either tried previously or were being prescribed as a current medication. In a small number of cases intravenous immunoglobulin was given owing to a putative autoimmune aetiology. It can be inferred that steroids may also have been prescribed for these patients and possibly plasma exchange. However, no definitive comments can be made on immunomodulation administered to patients with bilateral HS as most centres did not document medications beyond conventional AEDs.

Co-morbidities

Many patients with bilateral HS had not undergone formal neuropsychometric testing and the data were often based on information from clinical letters. These data, though, were poorly captured and formal neuropsychometric scores were only rarely provided. Nonetheless, almost half of the patients were reported to have some cognitive impairment. In 17/96 (17.7%) memory impairment was specified while an additional 26/96 or 27.1% were reported to have cognitive difficulties although the specific nature of those difficulties was incompletely reported (21 intellectual difficulties and 5 non-specified cognitive impairment). One patient was reported to have learning difficulties, 3/96 (3.1%) had developmental delay and 1 patient had attention deficit hyperactivity disorder (ADHD) (Figure 3A). In 42 of the 96 cases (43.8%) there was no evidence for cognitive impairment and in 6 (6.3%) cases insufficient information was recorded.

Psychiatric co-morbidity (Figure 3B) was present in almost half of the patients (46/96, 47.9%), with particular representation of depression, anxiety or both. A small number (4/96, 4.2%) developed inter-ictal psychosis with an additional 4 patients having experienced post-ictal psychosis. Three patients had dissociative seizures (psychogenic non-epileptic seizures; non-epileptic attack disorder) and 2.1% (2/96) had misused recreational substances.

As well as the commonly reported cognitive and psychological co-morbidities, these patients experienced many other medical co-morbidities, particularly osteoporosis (6/96; 6.3%) and headache (5/96, 5.2%; data not shown).

Investigations

All patients had to have radiologically confirmed bilateral HS to be included in the study. MRI also revealed additional cavernomas in 3 (3.5%) patients, post-traumatic change in two (2.4%) and cortical dysplasia in one.

The majority of patients were admitted for video-telemetry (**85/96; 88.5%**). A wide range of both inter-ictal and ictal EEG findings were noted (Supporting Figure 2A and B). Thirty-six (37.5%) patients had bi-temporal interictal discharges and 24 (25.0%) had bilateral onset to seizures. **14/36 (38.9%) patients with bilateral temporal interictal discharges had no reported cognitive impairments. A total of 22/36 (61.1%) had cognitive impairment, intellectual disability, learning disability, or memory impairment. For those patients with bi-temporal onset to their seizures, 18/24 (75.0%) had cognitive impairment, intellectual disability, learning disability, or memory impairment. Only 6/24 (25%) patients with bilateral temporal seizure onsets had no reported cognitive impairments.**

Eleven (11.5%) patients underwent intracranial EEG recordings and of these the seizures had unilateral temporal onset in 5 (1 right, 4 left), bi-temporal onset in 4, unilateral hemispheric onset in 1, and multifocal onset in 1 (Table 1). Wada testing (sodium amobarbital) was not performed in many cases as the patient had already been determined to not be a candidate for surgical resection. In the 17 (17.7%) patients who did undergo a Wada test, a variety of findings were reported. While difficult to interpret in isolation, Wada testing did demonstrate left hemispheric dominance in most cases.

Surgical interventions

A total of 18 (18.75%) patients underwent epilepsy surgery. Of the eleven patients who underwent intracranial EEG monitoring, 4 subsequently had a resection (anterior temporal lobectomy [ATL], selective amygdalohippocampectomy [SAH], or corticectomy). Seven patients had single stage resections (Table 1). In 6 of the temporal lobectomies, hippocampal sclerosis was confirmed on pathological analysis with no histopathological data available for the other 2 cases. In the patient who underwent corticectomy, non-specific findings were demonstrated.

Outcomes

Outcome to the point of the most recent appointment in the EPIGEN centre was recorded (Figure 4). In 23 (24.0%) cases outcome data was not recorded and one patient died. Four patients were seizure free on anti-epileptic medication alone (4/96; 4.2%). Of the 11 patients who underwent surgical resection, only 1 patient was rendered completely seizure free, and 3 (27.3% of the patients who had undergone resection) showed improvement in seizure frequency.

Around a third of patients continued with medical management alone (34/96, 35.4%). There was also a proportion of patients who underwent, or are considering, neurostimulation therapy with either vagal nerve stimulation (9/96; 9.4 %), responsive neurostimulation (6/96; 6.3%) or, in one case, both.

Comparison of people with bilateral HS to those with unilateral HS

We specifically wished to delineate how specific certain key findings were to bilateral HS. We therefore compared our 96 patients with 201 cases of unilateral HS also obtained from participating EPIGEN Centres. The key phenotypic data from the patients with unilateral HS are highlighted in Table 2. As illustrated, patients with unilateral HS were significantly more likely to have experienced febrile seizures (44.3% in unilateral HS compared to 25% in bilateral HS; *p =0.0002*; Fisher's exact test) and were less likely to have experienced status epilepticus at any

point in their epilepsy history (11.4% in unilateral HS versus 27.1% in bilateral HS). While the Fisher's exact test suggests a highly significant difference with regards to status epilepticus, some caution must be applied as data on status epilepticus were not provided for over half of patients with unilateral HS. Also, whereas focal aware seizures were a common seizure type in patients with unilateral HS being found in 84 cases (41.8%), such seizures were less frequent in people with bilateral HS (*p=0.002*; Fisher's exact test) and no patient with bilateral disease had only focal aware seizures.

Discussion

The current study is the largest phenotypic characterisation of bilateral HS and epilepsy to date. Importantly, the study collates data from multiple epilepsy centres thereby reducing bias and also better reflecting 'real-life' clinical practice across multiple countries. Previous work[8–11] is summarised in Table 3 coupled with a summary of our data.

It is long recognised that the contralateral hippocampus in patients with unilateral hippocampal sclerosis may have imaging changes[12–15] or pathological features detected at post-mortem[16]. **Moreover, volumetry, particularly with appropriate normalisation to control values has been shown to enhance detection of bilateral hippocampal atrophy [13,15,17] while in studies of patients with unilateral HS, it has been demonstrated that the contralateral hippocampus is significantly smaller than control hippocampus although also larger than the hippocampus ipsilateral to the lobectomy, potentially best described as asymmetrical HS[15]. MR techniques have been utilised to try and refine bilateral mesial temporal lobe epilepsy and, for example, predict surgical outcome in patients with bilateral hippocampal atrophy[18]. There are also some patients with bilateral HS who are drug responsive. Inclusion of drug responsive cases or those with hippocampal atrophy defined by volumetric or more sophisticated MR analysis would have increased the number of**

people studied, but our aim was to better describe patients with pharmacoresistant epilepsy and clear-cut bilateral HS visible on MR imaging in a standard clinical setting. We wished to record and evaluate current clinical practice and to determine whether detailed phenotypic analysis might offer insights to improve clinical care going forwards

Of the 96 patients we studied, the majority were Caucasian and spanned a wide age range. The patients in this cohort had pharmacoresistant epilepsy and most patients had: 1) a very high number of seizures per month, 2) previous exposure to multiple AEDs and 3) were on average taking around three AEDs concurrently. The pattern of drug prescription likely reflects trends in clinical practice. The study was a retrospective review of medical records, and some patients had very long epilepsy histories. It is, therefore, perhaps unsurprising that a majority of patients had been exposed to carbamazepine although this was not a common current prescription with levetiracetam and lamotrigine now being favoured.

Intriguingly no patient with bilateral HS had only focal aware seizures and the incidence of focal aware seizures overall (i.e. even when considered in combination with other seizure types) was also significantly lower than in patients with unilateral HS. The exact reasons for this are uncertain. It might, for example, be that an individual seizure from a diseased hippocampus will likely cause impairment of awareness in the presence of an anatomically abnormal contralateral hippocampus.

Complex febrile seizures (either prolonged convulsion, convulsion associated with unilateral weakness or febrile status epilepticus in childhood) associate with an increased risk of subsequently developing epilepsy [19,20]. Some studies have reported an incidence of febrile seizures of up to nearly 50% in patients with unilateral HS[21] **and our data found an incidence of febrile seizures of 44.3% in unilateral HS. Similarly, previous work has shown that in patients with temporal lobe epilepsy and a background of febrile convulsions that majority will have unilateral hippocampal atrophy[17].** This does not seem to be recapitulated in bilateral HS. As in other work[10] a relatively smaller proportion of our patients with bilateral HS had a history of febrile seizures (26%) and only two cases in this

cohort had prolonged febrile convulsions. It was noted that 5 patients with febrile seizures also had a family history of epilepsy although full information about family history of epilepsy may be lacking as the study was a retrospective review of available data rather than prospective acquisition of detailed family pedigrees. Previous genome-wide association studies have suggested a possible association of mesial temporal lobe epilepsy in patients who have previously had febrile convulsions and mutations in the *SCN1A* gene[22]. However, in the current work those who did have a history of febrile seizures often also had other risk factors for developing bilateral HS, for example a subsequent meningoencephalitic illness.

While chronic epilepsy, even in patients with pre-existing hippocampal malformations, does not necessarily result in HS[23], it is also well recognised that prolonged status epilepticus can result in profound hippocampal volume loss and associate with subsequent pharmacoresistant epilepsy[24]. Although patients from the latter category are represented in the current cohort, for example the 3 patients in whom NORSE was recorded as the underlying aetiology, most patients did not have a history of status epilepticus. The most common aetiology cited by investigators was infection and **other work has also demonstrated that bilateral hippocampal atrophy may be more likely after a meningitic or encephalitic illness**[17]. A small number of patients were demonstrated to have a potentially causal antibody, but this proportion may be higher in future studies as more antibodies implicated in the pathogenesis of epilepsy are identified and testing for such antibodies increases.

Despite the large number of cases included here, it is not possible to define an exact aetiology for bilateral HS. There are features to suggest that bilateral HS is a different entity to unilateral HS, but it may be that bilateral hippocampal damage represents the final common pathway of a heterogeneous collection of rare epilepsy syndromes. Similar to the increasing recognition that antibody-mediated disease may contribute to refractory status epilepticus, it can be speculated that certain insults, perhaps particularly infection, may lead to development of bilateral HS in people with a genetic susceptibility to this condition

As would be predicted in a group of patients with pharmacoresistant epilepsy, there were high rates of cognitive and psychological co-morbidity. The current study reviewed available data and therefore only possible surgical candidates may have had detailed neuropsychometric testing. Were all patients to be formally tested, the rates of recorded cognitive impairment might be higher, particularly as in cases of unilateral HS patients may be below the 50th centile in all cognitive domains[25]. There was also a high rate of psychopathology with over a third of patients reporting depression, anxiety or both. Again, one may predict higher rates of psychiatric symptomatology were this to be formally evaluated for all patients.

Only 11 (11.5%) patients proceeded to epilepsy surgery, which is low compared to other studies that have specifically reviewed surgical case series of HS. **In 1996, Arruda and colleagues evaluated 74 consecutive patients with mesial temporal lobe epilepsy undergoing surgical resection. When measured by volumetry, 17 of these cases had bilateral hippocampal atrophy and while the outcomes in this group were less favourable than in unilateral HS, 61.7% had class I or II outcome according to Engel's modified classification[26].** More recently, Vanli-Yuvaz and colleagues reviewed 124 patients who had undergone epilepsy surgery for hippocampal sclerosis at their centre in Turkey[11]. In that study 93 patients had unilateral HS and 31 had bilateral HS. The authors report that 16.1% of bilateral HS were not pharmacoresistant and that six of nine patients with bilateral HS who underwent unilateral temporal lobectomy were rendered seizure free[11]. Similarly in 2013 Malter and colleagues evaluated patients at a single centre in Germany[9]. They also identified 31 cases of bilateral HS and eleven of these proceeded to surgery with resection of the putatively more epileptogenic sclerosed hippocampus. Of those that did progress to surgery, seizure freedom rates at 12 and 24 months were similar to cases of unilateral HS and no patient with bilateral HS that underwent resection became globally amnestic. The authors did caution that results in such small numbers could not be more widely extrapolated. An older study evaluated 28 patients with bilateral independent temporal lobe seizures detected with intracranial recording of whom 15 proceeded to resection[27]. Ten patients were rendered seizure free and of those seven were shown to have

unilateral HS on imaging or a lateralised Wada result. In the five who had persistent seizures, such structural or functional lateralisation was not evident[27].

In the current study only a single patient who underwent resective epilepsy surgery became seizure free post-operatively. The reasons for this relatively low percentage of operated cases may be multifactorial including patient choice, physician choice and increasing availability of other therapies, particularly new AEDs and neurostimulation. Additionally, in our cohort, very few patients (17/96; 17.7%) had clear evidence of unilateral temporal lobe epilepsy on non-invasive video-telemetry while 24 patients (25%) had evidence of bilateral temporal lobe seizures. This may in turn account for the lower number of patients proposed for invasive investigations with Wada testing being performed in only 17/96 (17.7%) and intracranial recording in 11 patients (11.5%).

While the previously published surgical case series have reported good seizure outcomes[9,11], there is concern that unilateral resection in patients with bilateral HS, even if the patient is rendered seizure free, can compromise remaining memory function[27,28]. Moreover, there is also now increased understanding that patients with bilateral mesial temporal lobe epilepsy can have independent seizure generation in each hippocampus on a cyclical basis. Studies with ambulatory electrocorticography recorded from Neuropace Responsive Neurostimulation devices have shown that seizures may arise for several weeks in one hippocampus before then switching to the other [29,30]. Given that video-telemetry is typically of one to two weeks' duration, this may artificially skew interpretation if all, or most, of the seizures during EEG recording happen to arise from one of the sclerosed hippocampi.

At a pathological level, those patients who underwent temporal lobectomy were found to have HS on histopathological examination, where this was available. Interesting work has shown that in post-mortem cases of HS there can be bilateral accumulation of tau deposits within the sclerosed hippocampus[31] and bilateral dentate granule cell dispersion[16]. The contributions that such bilateral

pathology may make to cognitive difficulties and/or epileptogenesis, particularly in patients in whom bilateral HS is detected *in vivo* would be worthy of further investigation.

Although clearly limited as a retrospective review of patient notes, the current work would suggest that proceeding to resection in patients with bilateral HS is not that common in real life practice and perhaps viewed more as a palliative, rather than a curative, procedure, even in specialist centres that are able offer the range of epilepsy surgeries available. **Moreover, the presence or absence of focal aware seizures might be valuable in stratifying potential epilepsy surgical candidates going forwards. For example, the presence of focal aware seizures might be indicative of unilateral HS and, perhaps more importantly, the absence of focal aware seizures in a patient without obvious markers of bilateral HS might be indicative of bilateral disease and consequently a poorer post-operative prognosis. Careful delineation of seizure phenotype could therefore offer insights into the possibility of sub-clinical bilateral disease, just as Penfield was attuned to so many years ago.**

Limitations

This study was limited to retrospective review of patient data held at the individual EPIGEN centres. Despite making data entry fields formulaic, there were inevitable subjective differences in the way individual investigators entered data into each field. While objective information was provided for the majority/all patients for certain fields (for example seizure type and medications), more subjective data fields such as cognitive and psychological difficulties were less complete thereby potentially limiting interpretation. A well-defined multi-centre prospective study examining patients with bilateral HS would seem worthwhile.

Conclusions

Patients with pharmacoresistant epilepsy and bilateral HS can pose significant challenges to clinicians trying to ameliorate both seizures and associated co-morbidities. In the current study, which samples clinical practice across multiple centres in different countries, such patients are shown to: 1) have frequent seizures with no patient having focal aware seizures alone; 2) have a relatively low frequency of febrile seizures compared to unilateral HS; 3) often have no identified etiology to the bilateral HS and 4) do not often proceed to surgical resection. A prospective study examining a large series of cases with bilateral HS, building on data presented here, would help to better inform etiology as, for example, antibody testing becomes more established. Similarly, genomic work in a well phenotyped group of patients with bilateral HS might provide further distinctions from unilateral HS. Epidemiological work is also required to better determine whether a more aggressive or more circumspect approach is appropriate when deciding to offer unilateral hippocampectomy in patients with bilateral disease.

Acknowledgements:

The research was supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC)

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.

None of the authors declare any conflicts of interest

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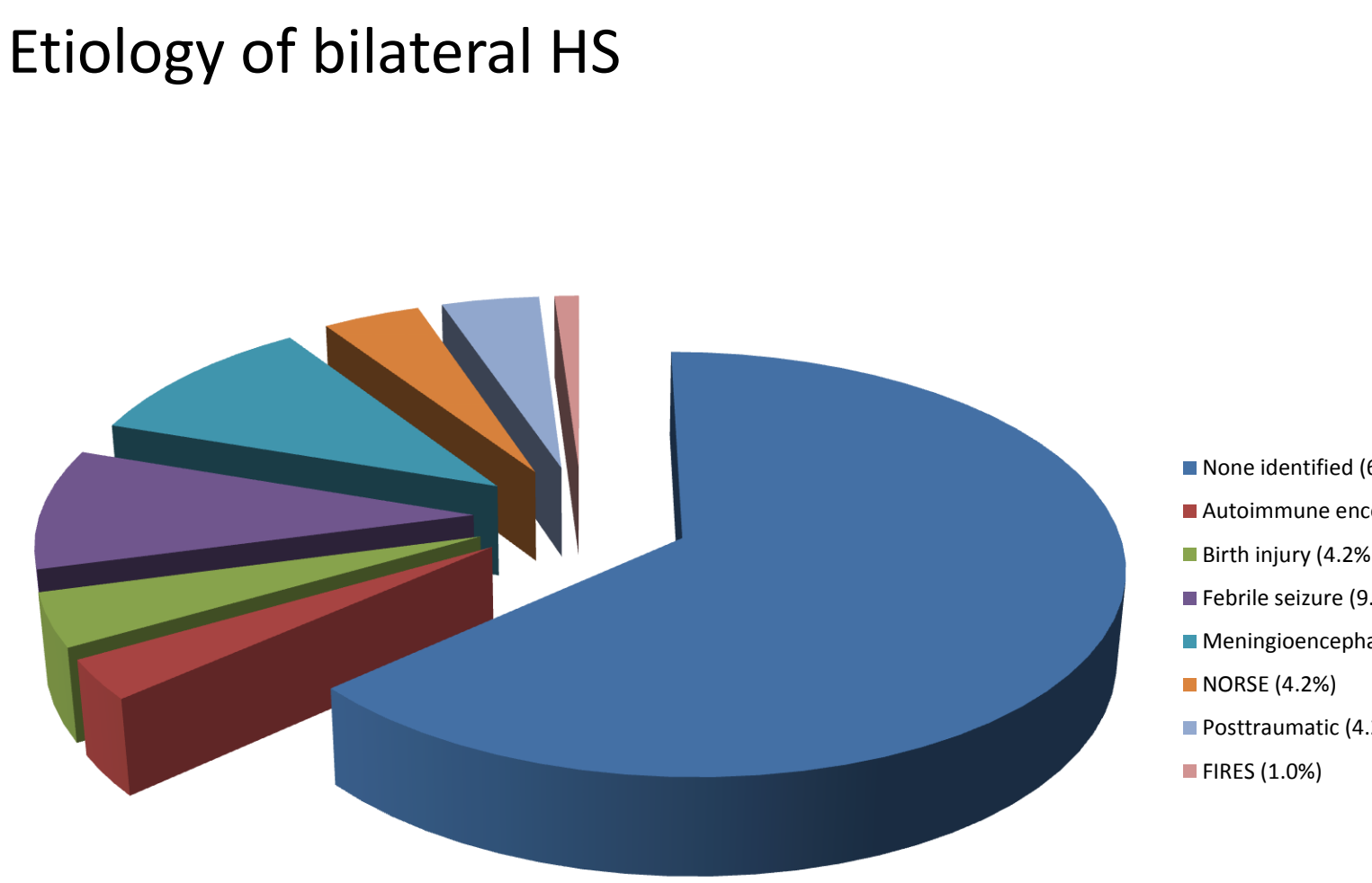


Figure 1: Etiology of bilateral HS

The causes of hippocampal sclerosis were identified by referring centers. In almost two thirds of patients, no clear cause
Infective etiologies and febrile seizures were the main attributable causes with small numbers of patients developing bi
following birth injury, brain trauma, putative antibody-mediated disease, new onset refractory status epilepticus (NORS
infection-related epilepsy syndrome (FIRES).

Previously tried medications

2A

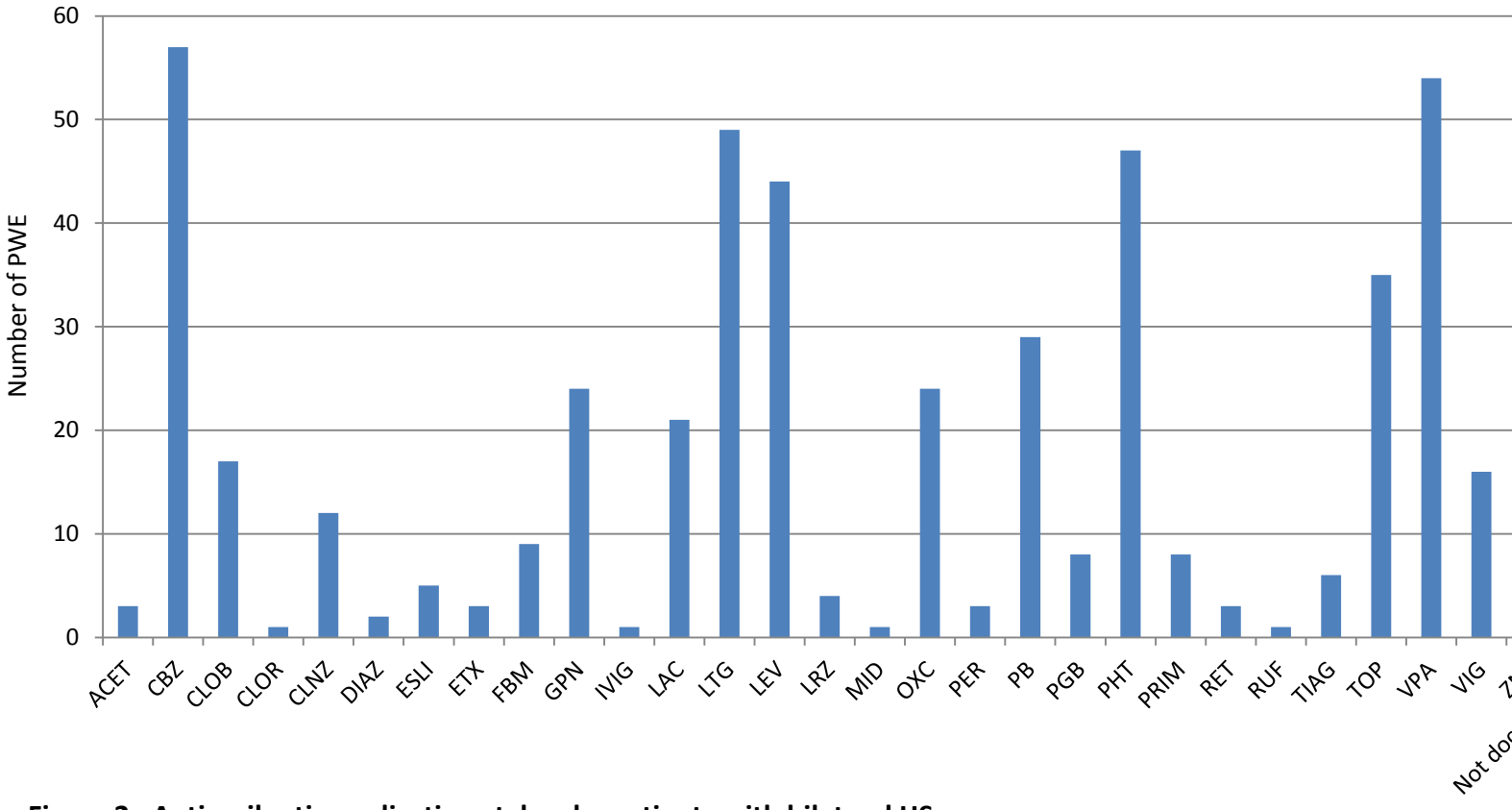


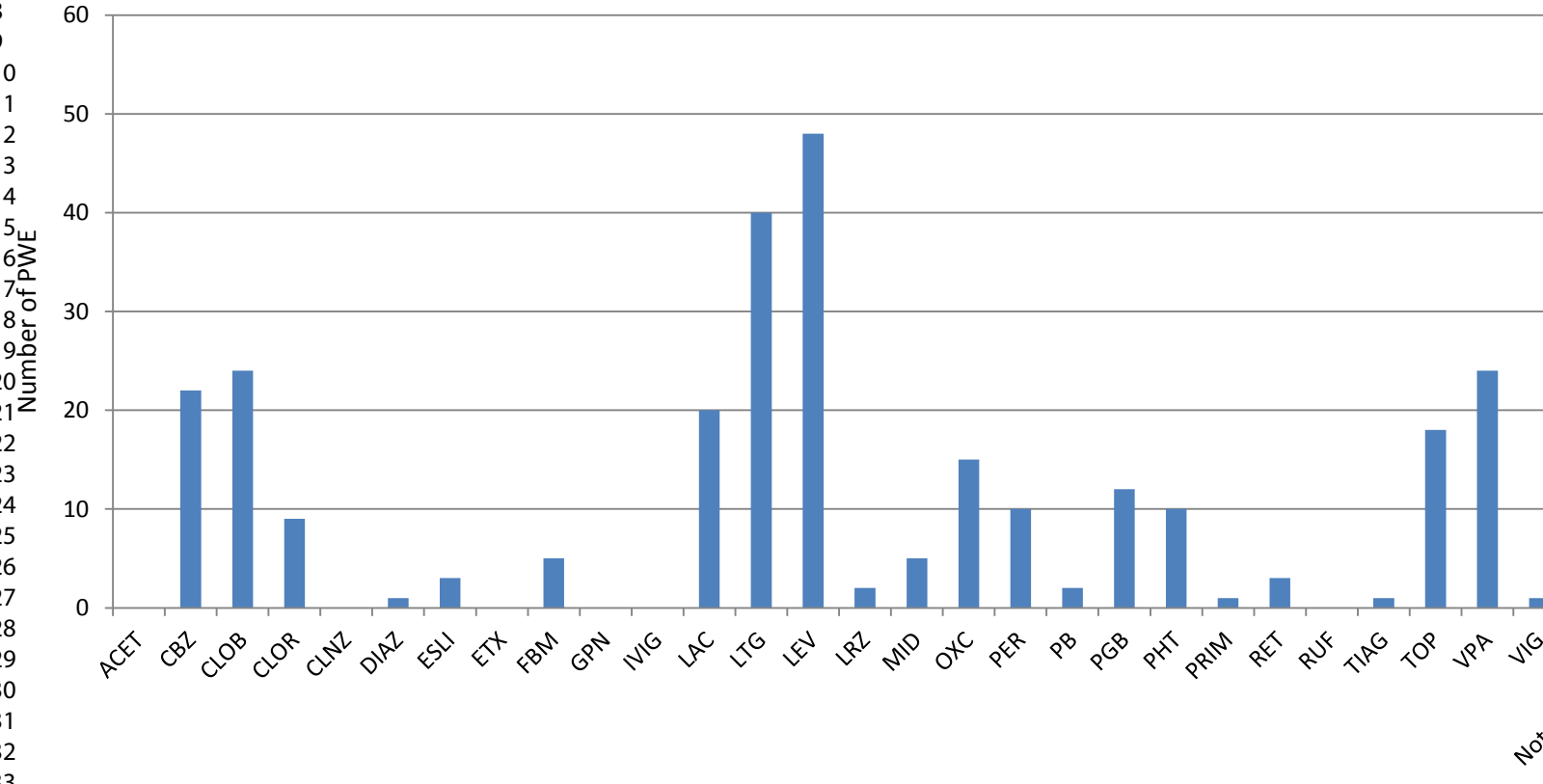
Figure 2: Anti-epileptic medications taken by patients with bilateral HS

The cohort of patients studied had severe drug resistant epilepsy having tried an average of 5.4 medications previously mean number of currently taken medications being 2.9 (B). A wide variety of medications had been trialled, predomina recommended for treatment of focal epilepsy.

Abbreviations: ACET (acetazolamide); CBZ (carbamazepine); CLOB (clobazam); CLOR (clorazepate), CLNZ (clonazepam); DIAZ (diazepam); ESLI (eslicarbazepine) (ethosuximide); FBM (felbamate); GPN (gabapentin); IVIG (intravenous immunoglobulin), LAC (lacosamide); LEV (levetiracetam); LRZ (lorazepam); LTG (lamotri (midazolam); OXC (oxcarbazepine); PER (perampanel); PB (phenobarbital), PGB (pregabalin); PHT (phenytoin), PRIM (primidone); RET (retigabine); RUF (rufinar (tiagabine); TOP (topiramate); VPA (valproate); VIG (vigabatrin); ZNS(zonisamide). PWE (persons with epilepsy)

Current medications

2B



Cognitive and psychiatric comorbidities

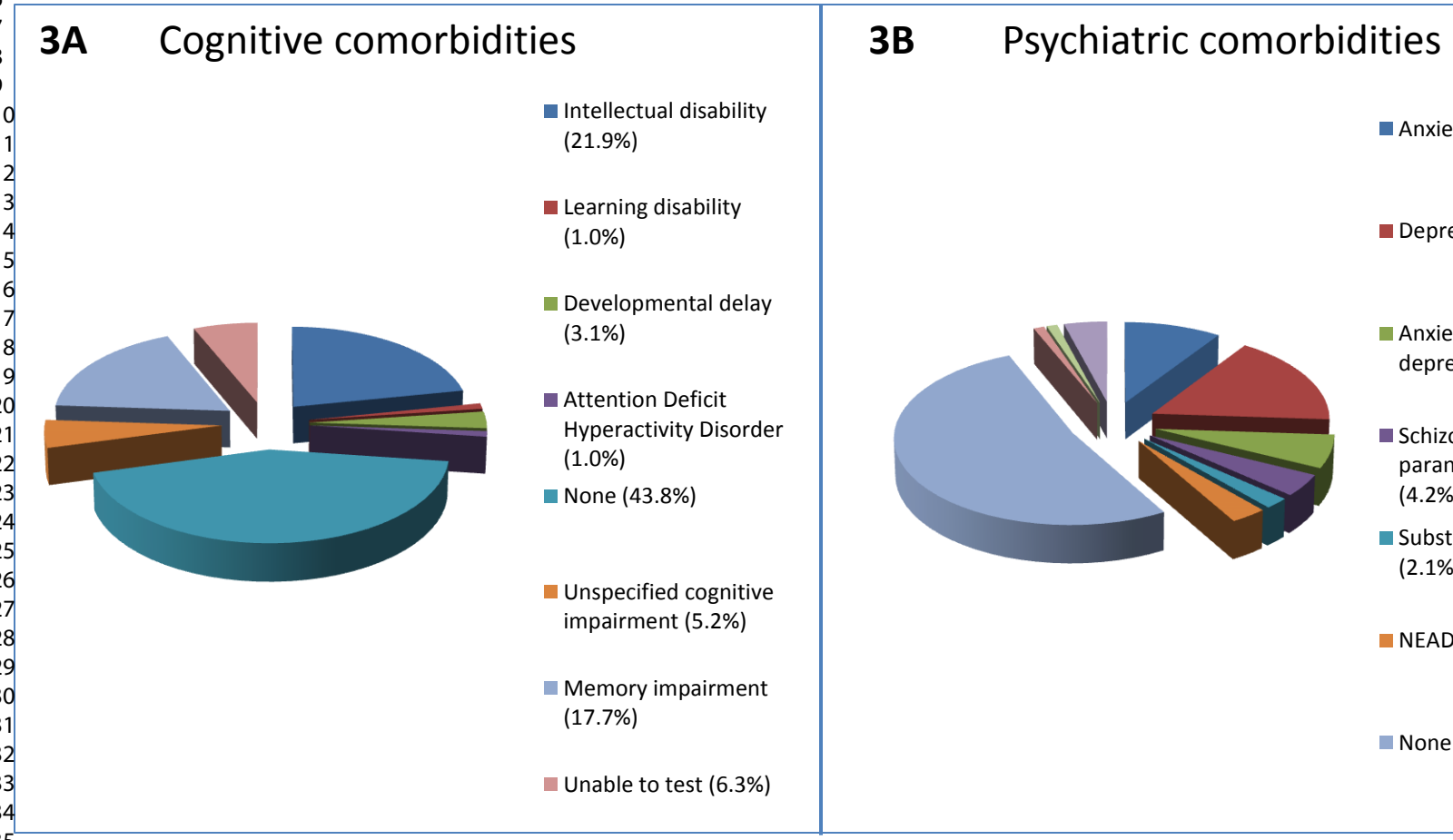


Figure 3: Comorbidity in patients with bilateral HS

Cognitive (3A) and psychiatric (3B) co-morbidities occurred commonly in persons with bilateral HS. Twenty-one patients intellectual disability, and 17 had memory impairment. The most common psychiatric comorbidity was depression with anxiety. A small percentage of patients experienced psychosis and two patients had abused recreational substances

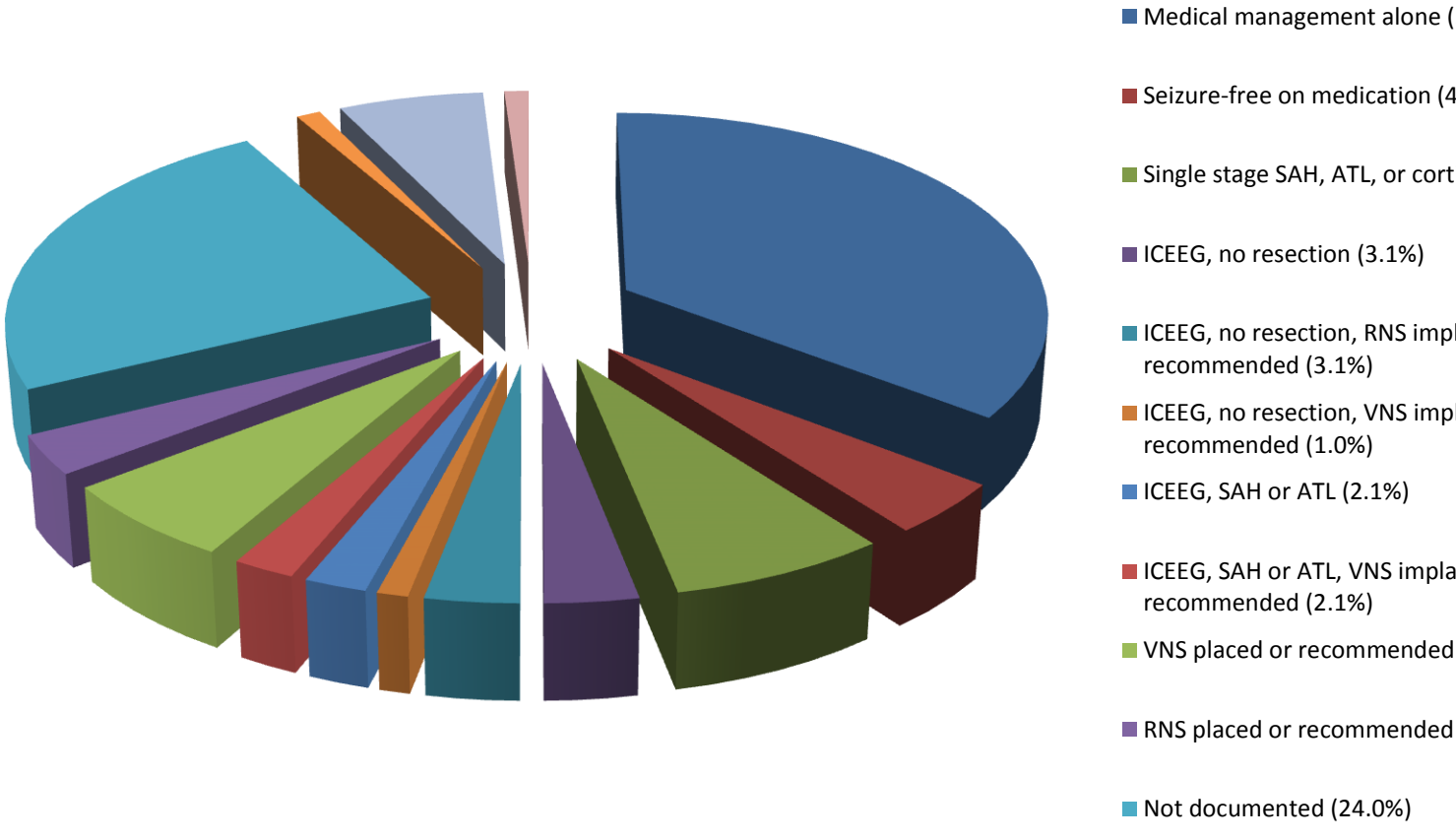


Figure 4: Overall outcomes in patients with bilateral HS

The majority of patients with bilateral HS persisted with medical treatment alone. Eleven patients had resective surgery
anterior temporal lobectomy (ATL), selective amygdalohippocampectomy (SAH), or corticectomy; 4 underwent prior intra
monitoring (ICEEG) and 7 patients had single stage resections. Seven underwent ICEEG without subsequent resection. Six
had undergone, or were awaiting, neurostimulation. Four (4.2%) became seizure-free on medication alone.

Table 1. Clinical characteristics of patients with bilateral HS who underwent ICEEG or resective surgery

Demographics: sex, duration of epilepsy	Scalp EEG	ICEEG*	Wada test	Surgical resection	Pathology	Outcome ***
Male, 16 years	Bilateral independent temporal epileptiform discharges and seizure onsets	Bilateral multifocal seizure onsets	Not performed	No	N/A	Not seizure free, RNS recommended
Male, 14 years	Bitemporal epileptiform discharges, left temporal seizure onsets	Left temporal seizure onsets	Performed but data not available	No	NA	Not seizure free
Male, 34 years	Bitemporal epileptiform discharges	Right temporal onset seizures	Not performed	No	N/A	Not seizure free
Male, 21 years	Left temporal epileptiform dicharges and left temporal seizure onsets	Bilateral independent, bisynchronous interictal discharges; bilateral independent and bisynchronous ictal onsets	Left language dominance, right hemisphere memory impairment	No	N/A	Not seizure free, RNS recommended
Female, 20 years	Bilateral temporal epileptiform discharges and seizure onsets	Bitemporal	Left language dominance, intact memory bilaterally	No	N/A	Not seizure free
Female, 22 years	Bilateral independent temporal epileptiform discharges, left-sided and nonlateralizable seizure onsets	Left temporal seizure onsets	Not performed	No	N/A	Not seizure free, RNS implanted
Male, 20 years	Left anterior-mid temporal epileptiform discharges, left temporal onset seizures	No	Left hemisphere language dominance; memory scores not documented	Left selective hippocampectomy	Moderate mesial temporal sclerosis (MTS)	Not seizure free
Female, 33 years	Left temporal epileptiform discharges, left temporal onset seizures**	No	None	Prior right temporal lobectomy; no new surgical resection	Not documented	Not seizure free
Female, 53 years	Not documented	No	“normal right sided Wada”	Right temporal neocorticectomy	No evidence of inflammation, tumor, or congenital malformation	Not seizure free
Male, 44 years	Right midtemporal and bilateral independent frontotemporal epileptiform discharges, right temporal onset seizures	No	Performed but data not available	Right temporal lobectomy	Mesial temporal sclerosis	Reduced but not seizure free

Male, 48 years	Bilateral temporal epileptiform discharges, right temporal onset seizures	No	Left hemisphere language dominance, right hemisphere memory impairment	Right selective amygadalo-hippocampectomy with subsequent temporal lobectomy	Hippocampal sclerosis	Reduced but not seizure free
Male, 63 years	Bilateral independent temporal epileptiform discharges, left temporal and bitemporal onset seizures	No	Left hemisphere language dominance, intact memory bilaterally	Left selective amygdalo-hippocampectomy	Severe hippocampal sclerosis	Dramatically improved but not seizure free
Female, 60 years	No interictal epileptiform abnormalities, left temporal onset seizures	No	Not performed	Left temporal lobectomy	Pathology not available	Not seizure free
Male, 22 years	Left temporal epileptiform discharges, nonlateralizable seizure onsets	Diffuse left hemispheric seizure onsets	Not performed	Prior corpus callosotomy; no new surgical resection	N/A	Not seizure free.
Male, 13 years	Bilateral independent temporal epileptiform discharges and seizure onsets	Bilateral temporal seizure onsets, right > left	Left hemisphere language dominance, bilateral memory impairment	Right temporal lobectomy	MTS; malformation of cortical development Palmini grade I	Not seizure free, VNS implanted
Male, 4 years	Bilateral independent temporal epileptiform discharges and seizure onsets	Left temporal seizure onsets	Not performed	Left temporal lobectomy	Severe MTS; focal cortical dysplasia and microdysgenesis	Not seizure free. VNS recommended.
Female, 36 years	Left temporal and bisynchronous temporal epileptiform discharges; broad left hemispheric seizure onsets	Left temporal discharges, left temporal seizure onset	Left hemisphere language dominance, bilateral memory impairment	Left temporal lobectomy	Severe MTS; malformation of cortical development Palmini IA	Seizure free
Female, 23 years	Left temporal epileptiform discharges, broad left hemispheric seizure onsets	Bilateral temporal seizure onsets, left > right	Bilateral language dominance, bilateral memory dysfunction	Left temporal lobectomy	Severe MTS; malformation of cortical development Palmini II	Lost to follow up

*Intracranial EEG

**EEG data recorded following right temporal lobectomy, essentially demonstrating contralateral temporal lobe seizures

***Note that there was insufficient data to ascribe appropriate Engel outcome

Table 2: Comparison of clinical characteristics between unilateral HS (n=201) vs bilateral HS cases (n=96).

	Unilateral HS (n=201)	Bilateral HS (n=96)	*P value*
History of febrile seizures			0.000236
Yes	89 (44.3%)	24 (25%)	
No	81 (40.3%)	63 (65.6%)	
No data	31 (15.4%)	9 (9.4%)	
History of status epilepticus			< 0.00001
Yes	23 (11.4%)	26 (27.1%)	
No	69 (34.3%)	64 (66.7%)	
No data	109 (54.2%)	6 (6.2%)	
Focal aware seizures*			0.002011
Yes	84 (41.8%)	21 (21.9%)	
No	106 (52.7%)	71 (73.9%)	
No data	11 (5.5%)	4 (4.2%)	
Focal impaired awareness seizures			0.474705
Yes	191 (95%)	88 (91.7%)	
No	6 (3%)	4 (4.2%)	
No data	4 (2%)	4 (4.2%)	
Focal to bilateral tonic-clonic seizures			0.993164
Yes	131 (66.7%)	64 (66.7%)	
No	59 (29.4%)	28 (29.2%)	
No data	8 (4%)	4 (4.2%)	

Publication	Phenotype(s)	Mean duration of epilepsy, years (range)	History of FC	History of SE or FSE	e
Ravat et al.[8]	35 patients with bHS	15.7 (2-47)	19 (54.3%) history of FC		4 (11. of enc
Malter et al.[9]	Total of 322 patients: 31 with bHS, 291 with uHS	11 (2-55) with bHS and 22 (0-65) with uHS (p=0.08, Fisher's exact test)	8 (26%) with bHS and 69 (24%) with uHS had FC (p=0.024, Fisher's exact test)	3 (9.5%) of bHS and 1 (0.3%) of uHS had SE (p<0.001, Fisher's exact test)	8 (26% 57 (20 had e (p=0.4 test)
Van Paesschen et al.[10]	Total of 100 patients: 7 with bHS, 41 with uHS, 5 with anterior hippocampal atrophy, 47 with other findings	28 (1-36) with bHS, 20 (1-42) with uHS, 15 (10-17) with anterior hippocampal atrophy (not significant)	0 (0%) with bHS, 21 (50%) with uHS, and 4 (80%) with anterior hippocampal atrophy had FC (p=0.00002, Fisher's exact test)		3 (43% (12%) (0%) w hippo had e signifi
Vanli-Yavuz et al.[11]	Total of 124 patients: 31 with bHS, 93 with uHS		20 (64.5%) with bHS and 60 (64.5%) with uHS had FC (not significant)	10 with bHS (32.3%) and 9 (9.7%) of uHS had history of SE (p=0.007, Fisher's exact test) 10 with bHS (32.3%) and 9 (9.7%) with uHS had history of FSE with FSE (p=0.002, Fisher's exact test) *3 patients had history of both SE and FSE	
Current series	96 patients with bHS	30.4 (1-79)	24 (25.0%) with history of FC	26 (27.0%) with history of SE	10 (10 histor menin

Table 3: Comparison of large case series of bilateral HS

bHS: bilateral hippocampal sclerosis; uHS: unilateral hippocampal sclerosis; FC: febrile convulsion; SE: status epilepticus; FSE: febrile s