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Narrative Review

A New Perspective on Dual Pathology in Epilepsy

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Abstract

The approach to dual pathology in drug-resistant epilepsy is a challenging issue for clinicians. The main aim is to precisely determine and resect the epileptogenic focus, which is commonly complicated by the limitations of scalp-EEG monitoring, the restricted availability of intracranial EEG recording, the indecision to select between staged surgery and dual lesionectomy, and encountering with the possible postsurgical deficits. Previous studies with a focus on the management of dual pathology have certain limitations, such as the enrolment of mixed groups of patients, imprecise reports of EEG findings, a lack of control groups, short-term follow-ups, and limited reports of postsurgical neuropsychological evaluations and deficits. In this manuscript, I have suggested a classification that has mainly addressed dual pathologies containing hippocampal sclerosis —the most common dilemma for epileptologists — and I have tried to divide them in a practical way for both clinicians and researchers. Lesions other than hippocampal sclerosis have also been considered to show the essential need to revise the definition of dual pathology and to encourage researchers to approach them as a distinct and important category. Moreover, the classification has mentioned multiple pathologies and categorized them into commonly encountered subgroups. It seems that using this classification to categorize dual and multiple pathologies based on anatomical characteristics and findings of presurgical evaluation might be helpful to design more targeted studies on homogenous groups of patients and simplify uniform planning.

Keywords: Dual Pathology, Epilepsy, Hippocampal Sclerosis, Surgery

Introduction

The approach to dual pathology (DuP) in epilepsy has been a matter of debate for a long time. The definition is commonly applied to the coexistence of hippocampal sclerosis (HS) with another epileptogenic lesion in the ipsilateral hemisphere detected by neuroimaging or pathologic study.[1,2] Coexistence of two etiologically independent pathologies excluding HS has been called double pathology (DoP).[3] However, semantically, DuP or DoP could be established to describe the presence of any two pathologies in any location, with the potential to act as a seizure onset zone (SOZ).

Finding two pathologies in magnetic resonance imaging (MRI) of patients with intractable epilepsy is often a challenging dilemma addressed by many studies. Though drawing a conclusion from current studies is still difficult due to potential limitations. Many studies have enrolled a few patients, including both pediatric and adult groups. Methodological limitations such as retrospective views of studies, lack of control groups, selection bias, and individualized decision-making have decreased the reliability of results. Many studies have not presented detailed findings of scalp electro-encephalography (EEG) monitoring, neuropsychiatric tests, and long-term post-surgical outcomes. Moreover, the limited use of intracranial EEG (iEEG) recording has restricted the assessment of the epileptogenic potential of lesions, which is among the most important factors in surgery planning.

In this paper, a classification system for two and more pathologies based on anatomical characteristics and findings of presurgical evaluation has been suggested (Table 1). Using this classification, I tried to sort out the different possibilities of DuP and DoP and discuss the current approaches for each group. Categorization of these conditions might help to overcome the current ambiguity in approach to more than one lesion, help to design more targeted studies on homogenous groups of patients, and simplify uniform planning.

This classification has mainly addressed DuP, which

is the most common dilemma for epileptologists, and has tried to divide it in a practical way for both clinicians and researchers. Lesions other than HS have also been considered in order to encourage the researchers to approach them as a distinct and important category. Finally, the classification has mentioned multiple pathologies and categorized them into commonly encountered subgroups.

Table 1. Classification of Two and More Pathologies

Dual Pathology
1.Unilateral HS and extrahippocampal temporal lesion
1. MRI-visible lesion[a] and HS
a. Epileptogenic hippocampus and lesion or indistinguishable
b. Epileptogenic hippocampus
c. Epileptogenic lesion
2. MRI-invisible second pathology
a. Epileptogenic HS and evidence[b] of an invisible epileptogenic lesion
b. Non-epileptogenic HS and evidence of an invisible epileptogenic lesion
c. Epileptogenic lesion and invisible epileptogenic HS
d. Non-epileptogenic lesion and invisible epileptogenic HS
2. Unilateral HS and extratemporal or contralateral extrahippocampal lesion
1. MRI-visible lesion and HS
a. Epileptogenic hippocampus and lesion[c]
b. Epileptogenic hippocampus
c. Epileptogenic lesion
2. MRI-invisible second pathology
a. Epileptogenic HS and evidence of an invisible epileptogenic lesion
b. Non-epileptogenic HS and evidence of an invisible epileptogenic lesion
c. Epileptogenic lesion and invisible epileptogenic HS
d. Non-epileptogenic lesion and invisible epileptogenic HS
Bilateral HS
1. MRI-visible bilateral HS
a. Unilateral epileptogenic focus
b. Bilateral epileptogenic focus
2. MRI-visible unilateral HS
a. Bilateral epileptogenic focus
b. Contralateral epileptogenic focus
Double pathology (two extrahippocampal lesions)
1. Same lobe
2. Different lobes
Multiple pathologies
1. ≥3 extrahippocampal lesions
2. Unilateral/bilateral HS and other lesions

[a] MRI-visible lesion is defined as a potentially epileptogenic lesion which has been detected by a dedicated MRI of at least 1.5 Tesla and has been reported by an experienced neuroradiologist.
[b] Evidence of epileptogenicity needs confirmation by EEG monitoring and other imaging modalities (PET, SPECT, etc.) and/or surgical pathology.
[c] Lesions which involve both temporal and extratemporal lobes are classified based on the anatomical site of the most prominent part.

Dual Pathology

Unilateral HS and Extrahippocampal Temporal Lesion

MRI-Visible Lesion and HS

Coexistence of HS with other pathologies is a common finding in MRIs of patients with refractory epilepsy.[4,5] These lesions often include malformations of cortical development, tumors, glial scars, ischemic lesions, and vascular malformations.[2,6-8] In a complete setting of presurgical evaluation, including iEEG recording, which provides certain evidence of epileptogenicity for both the HS and the lesion, the removal of both epileptogenic zones seems reasonable. Removal of epileptogenic lesion is the main goal in epilepsy surgery, but if habitual seizures of the patient only arise from one of these lesions, resection of the responsible lesion and leaving the other one with a low threshold for epileptogenicity seems insecure. The pattern and distribution of interictal and ictal discharges in scalp-EEG might provide clues to the main source of epileptogenicity but often fails to distinguish a certain epileptogenic lesion, particularly when the lesion and HS are spatially close to each other.[1] Hence, despite limited utilization of iEEG and incomplete presentation of scalp-EEG findings in their surveys, many epilepsy surgery teams have reported better postsurgical outcomes after dual-resection surgery.[8-16]

Other than the results of uncontrolled trials, this approach could be supported by at least two other reasons. First, leaving a potentially epileptogenic

lesion that is not currently active might lead to a subsequent period of intractable epilepsy, which, after the imposition of a heavy socioeconomic burden, will result in a second surgery. Secondly, the limitations of scalp-EEG in the detection and differentiation of the epileptogenic lesion might inadvertently lead to the detection of one epileptogenic focus while the other could only be recognized by iEEG.

On the other hand, post-operative functional deficit, the most prominent limiting factor for the extent of surgery, has not sufficiently been addressed in studies with dual resection. Particularly when DuP includes focal cortical dysplasia (FCD) and mild HS, which is in favor of a higher possibility for epileptogenic role of FCD, resection of a functional hippocampus, albeit removing a probably second epileptogenic focus, might lead to significant postsurgical deficits.[17] However, there are few studies that have reported no difference between the post-surgical cognitive state of patients with DuP (FCD and HS) and those with HS after standard ATL[18] or even shown a better cognitive outcome in the former group.[19]

Although there is no consensus yet, it could be suggested that if both HS and the lesion are epileptogenic or the epileptogenic zone could not be localized to one of the lesions based on scalp-EEG (1.1.a), but both lesions could be resected without causing any significant deficit, dual resection seems reasonable.[20-22] If there is uncertainty about the epileptogenicity of both lesions and resection of each might cause an unacceptable postsurgical functional deficit, iEEG is preferred. There is insufficient data about the iEEG findings of patients who underwent single-lesionectomy surgery and experienced poor outcomes. Also, a detailed postsurgical neuropsychological evaluation of those who were treated by dual resection without conclusive evidence of epileptogenicity in both lesions is lacking.

Hence, to provide an evidence-based approach for subgroups 1.1.b and 1.1.c, it is necessary to conduct controlled studies addressing the long-term outcome of resecting the only iEEG-proven epileptogenic lesion. Also, an investigation of the pre- and post-surgical neuropsychological states of patients who have undergone dual resection will be useful to guide surgical decisions.

MRI-Invisible Second Pathology

The estimated sensitivity of MRI in detecting a second pathology in patients with HS is about 5-20%. Despite the lower incidence, vascular malformations and tumors have better chances of being diagnosed in comparison to FCDs.[11] The possibility of an MRI-invisible second pathology is often suspected when epileptologists detect interictal and ictal scalp EEG patterns or distributions that are disproportionate to the MRI-visible lesion. In these cases, other imaging modalities and iEEG are commonly used to confirm the existence of the other invisible epileptogenic lesion and guide the boundaries of surgical resection.[23] Imprecise findings of scalp EEG and limited use of iEEG might obscure the presence of a second lesion. Thus, the neglected second epileptogenic lesion is commonly found in pathological specimens or causes surgical failure.[24,25]

As expected, studies in which intraoperative electro-corticography has been routinely used[26] or their surgical approach for all patients has been anterior temporal lobectomy with amygdalohippocampectomy[11] have reported no prognostic role for DuP in patient group 1.2. But other studies that retrospectively reported the inability to detect and resect the second pathology considered it a leading cause of failure in temporal lobe epilepsy (TLE) surgery.[27] Due to the high prevalence of DuP, particularly in patients with TLE, consideration of this possibility in presurgical evaluation might lead to increased detection of the second pathology.[28]

Conducting retrospective studies on presurgical EEG-monitoring findings of patients with incidentally found DuP or those whose second pathology is confirmed by the next surgery might provide practical diagnostic clues. Using these clues could be useful in differentiating two temporal epileptogenic zones and helping the epilepsy surgery team choose ATL over SAH or lesionectomy when indicated.

The other dilemma is decision-making on single or dual lesionectomy in cases where the MRI-visible lesion shows no ictal/interictal discharges and the invisible lesion is the solitary epileptogenic focus. Diagnosis of an MRI-invisible epileptogenic focus that is located closely to a non-epileptogenic HS (1.2.b) is very difficult and often impossible based on scalp-EEG findings. However, when HS is evident in MRI and neuropsychiatric tests show relevant deficits, resection of both lesions commonly occurs by ATL based on scalp-EEG finding, and the second pathology is

detected in pathological study.[29]

If there is a visible HS in the MRI but the scalp-EEG findings show an unusual pattern in favor of a more posterolateral lesion that could not be resected by ATL, using iEEG would be helpful to detect DuP and guide the surgical boundaries. There is a general recommendation for dual lesionectomy in these patients, even if HS is not the SOZ.

When a lesion is close to mesial temporal structures with normal appearance in MRI and the epileptogenic zone is located in the ipsilateral temporal lobe based on scalp-EEG, some authors recommend resection of both the lesion and mesial structures on the non-dominant side if post-surgical deterioration of memory function is unlikely.[23] Due to the low ability of scalp-EEG in precise localization, this approach prevents missing an invisible epileptogenic hippocampus located near a visible epileptogenic lesion (1.2.c). Also, it should be considered that the lesion might have no epileptogenic potential, being located adjacent to an invisible SOZ in the hippocampus (1.2.d). The only certain way to determine the SOZ in these cases is using iEEG, as it is indicated when the lesion is far apart from mesial structures but the scalp-EEG findings are compatible with a mesial SOZ or if the lesion is close to the hippocampus of the dominant side. The results of neuropsychiatric tests in these two latter situations are determinant.

Unilateral HS and Extratemporal or Contralateral Extrahippocampal Lesion

MRI-Visible Lesion and HS

The coexistence of HS with an extratemporal lesion is not uncommon, but it is barely a direct target of studies in the literature. Surveys of the patients with mixed types one and two of the suggested classification have reported that hippocampal resection, together with lesionectomy, is associated with a higher chance of seizure freedom even in the absence of epileptogenic focus in the hippocampus.[1] As mentioned before, the rationale is not to leave a pre-epileptogenic HS, which would develop a new SOZ thereafter.[30]

Decision-making to perform a dual lesionectomy is simple when there is solid evidence of the role of both lesions in seizure occurrence. But the challenge is faced when one of the lesions does not show any abnormal activity in scalp-EEG or even intracranial recording.[31]

Hence, in order to make a relatively uniform decision, it is necessary to conduct studies that investigate the surgical outcome of patients who have an epileptogenic HS co-existing with a potentially epileptogenic extratemporal lesion without any ictal/interictal activity and vice versa.

MRI-Invisible Second Pathology

As mentioned before, the low sensitivity of MRI in detecting DuP sometimes leads to the use of other imaging modalities, such as iEEG, to determine and confirm the borders of an epileptogenic lesion, which only shows electrophysiological abnormalities. In contrast to part 1.2., where dual lesionectomy was more convenient, resection of an invisible extratemporal lesion based on scalp-EEG findings is not acceptable and certainly necessitates a comprehensive pre-surgical investigation and iEEG. This group of patients has not been specifically targeted in studies, possibly due to the low number and individualized decision-making. However, if the extratemporal contralateral epileptogenic zone is responsible for all seizures based on supplementary investigations, resection of HS might be postponed to the time of surgical failure.

Bilateral HS

MRI-Visible Bilateral HS

Evidence of bilateral temporal involvement is commonly observed in patients with TLE.[32] Scalp-EEG often shows bitemporal independent interictal epileptic discharges in these patients, and both temporal lobes might act as SOZs with unequal frequencies.[33] Moreover, abnormalities in both the hippocampi and temporal lobes have been shown frequently in structural and functional imaging modalities.[34-37] The best decision for the treatment of patients with bilateral TLE is still a matter of debate. Favorable post-surgical outcomes have been reported in some studies[38-41] and have been questioned by others.[42-44] Different inclusion criteria, presurgical evaluation methods, and follow-up periods in these studies have restricted the possibility of drawing a definite generalizable conclusion.

Unilateral Epileptogenic Focus

Older studies using only scalpEEG have reported poor surgical outcomes in patients with bilateral HS. However, in recent decades, results of iEEG have shown that in many patients with bilateral HS and

bitemporal ictal onset in scalp-EEG, only one temporal lobe is the responsible SOZ.[45-47] This finding has also been confirmed in patients with severe bilateral HS.[48] The best candidates for surgery among patients with bilateral HS are those whose scalp-EEG monitoring and other non-invasive presurgical evaluations point to one temporal lobe.[49] But controversy arises when presurgical findings are discordant, suggest different sides, or show bilateral involvement. According to EEG, the presence of bitemporal independent interictal spikes is generally reported and does not indicate a bilateral epileptogenic zone.[23] Using iEEG, previous studies have shown that in 44% of these patients, seizures originate from one temporal lobe, and in the other one third, more than 80% of seizures are unilateral.[50] Considering the irritative zone, more than 10% lateralization of interictal discharges on the contralateral side accompanies a less favorable surgical outcome.[51]

Unlike other dual pathologies, removal of the SOZ and leaving the other hippocampus behind is generally accepted in this circumstance, as bilateral hippocampectomy is not advisable due to severe functional impairment. However, the outcome is often inferior in comparison to patients with unilateral TLE.[52]

On the other hand, the vast amount of independent contralateral interictal discharges might point to a minor epileptogenic zone that will be activated spontaneously or by a post-surgical decrease in anti-seizure medications (ASMs). This potential epileptogenic zone could somewhat explain the lower success rate in these patients.[52]

The value of an irritative zone that is dominantly contralateral to the SOZ in surgical planning is yet to be determined. The necessity to proceed with iEEG when the scalp-EEG findings are in favor of unilateral SOZ but the other non-invasive evaluations present discordant data is controversial and needs to be clarified by a meta-analysis.

Bilateral Epileptogenic Focus

In patients with bilateral HS in MRI and seizures arising from both temporal lobes based on scalp-EEG findings (3.1.b), the workup often proceeds with iEEG, particularly if some other presurgical methods show any evidence of lateralization.[49]

In 25 to 30% of intracranial recordings, seizures arise independently from both temporal lobes.[53] Even in these patients, previous studies have reported considerable surgical success rates by resection of the lesion, which causes a higher seizure frequency or leads to more disabling seizures. Although not comparable with the prognosis of surgery in unilateral HS, a significant reduction in seizure frequency and improvement in quality of life have been reported in these patients.[38,39,45,54,55] However, neuropsychiatric findings and the possibility of postsurgical functional impairment, particularly in left-side resections, should be considered and could act as a limiting factor due to the significant impact of a functionally impaired hippocampus on quality of life.[56-58] It is necessary to conduct studies with a larger number of patients that directly address postsurgical quality of life in these patients and assess the risk-benefit of a potential reduction in memory function over better seizure control, mood improvement, and fewer drug side effects. Accordingly, decision-making in these cases should be individualized with accurate attention to electrophysiological and neuropsychiatric findings and their correlation to patients' clinical events and quality of life. Currently, in patients with independent bilateral TLE of no predominant epileptogenic side, treatment options other than surgery, such as neurostimulation, are generally recommended.[52]

MRI-Visible Unilateral HS

Bilateral Epileptogenic Focus

In patients with evidence of SOZ in both hippocampi, a visible unilateral HS in MRI often leads to resection of the lesion, particularly if it is associated with an ipsilateral deficit in neuropsychiatric function or confirmation by other non-invasive methods. Most of the previous studies have mentioned more favorable prognoses in these patients, but the number of cases is limited and the methods are various, with no clinical trial to address the issue.[23,52,53,59] On the other hand, ultra-reliance on MRI findings might lead to an unfavorable outcome.[60]

Further presurgical evaluation using PET, SPECT, fMRI, neuropsychiatric tests, and iEEG might show discordant findings in these cases. If the majority of findings are compatible with the apparent HS as the SOZ, surgical removal of the lesion is reasonable. But there are questions to be targeted in future clinical trials. What is the best decision if most of the findings other than EEG point to a SOZ contralateral to an MRI-visible HS? Moreover, if the advanced evaluations determined bilateral SOZ, should the existence of a

visible HS in the MRI lead to surgical resection?

Contralateral Epileptogenic Focus

The condition in which unilateral HS on MRI accompanies evidence of contralateral epileptogenic zone on scalp EEG, is commonly known as "burned-out hippocampus syndrome" (BHS) or "wasted hippocampus syndrome".[61] This phenomenon occurs in 3-7.5 % of patients with unilateral HS.[62]

BHS is not a real DuP, as the term is used when the evident HS in MRI is the real SOZ but the early propagation of the ictal discharges to the opposite side leads to a misdiagnosis of contralateral SOZ, by scalp-EEG. The irritative zone defined by scalp-EEG is often ipsilateral to real SOZ and iEEG localizes the ictal onset discharges to the sclerotic hippocampus confidently. Resection of the MRI-visible lesion has shown a good prognosis in these patients.[33]

Despite the high rate of concordance between iEEG-based SOZ and HS in MRI, there are few reported cases in which HS has been accompanied by evidence of contralateral SOZ in iEEG. In these patients, resection of the MRI-invisible SOZ has led to a favorable outcome despite a remaining contralateral HS. However, presurgical neuropsychiatric tests and functional MRI play an important role to preventing certain post-surgical functional deficits in these cases.

Observation of a sclerotic hippocampus in MRI is frequently in favor of the SOZ, particularly when it is concordant with the other electrophysiological findings, but in cases of any discrepancy, a more precise evaluation is necessary to determine the exact SOZ and exclude the presence of DuP.

Currently, the extent and invasiveness of the presurgical diagnostic methods needed for the patients in classification 2.b. are determined individually.

Two Extrahippocampal Lesions

Two extrahippocampal lesions with independent pathogenesis locating in the same lobe or different lobes have been defined as DoP.[63]

Since the approach to patients with drug-resistant epilepsy and two nonadjacent extrahippocampal lesions is not commonly influenced by having the same or different pathology, I suggest that the definition of DoP should not be dependent on pathogenesis. In order to prevent complications from using different terms, I also propose that DoP be accepted as a subtype of DuP in the next nomenclature.

For patients with DoP in the same lobe (Subgroup 1), dual lesionectomy is generally acceptable when scalp-EEG monitoring localizes the epileptogenic zone to the involved lobe, the lesions are close to each other, and they could be resected without any significant deficit. When the lesions are far apart and a dual lesionectomy might cause sequelae, intracranial recording is necessary to localize the epileptogenic lesion. However, in some patients, lesions are located in different unilateral or contralateral lobes (Subgroup 2). The necessity of using iEEG in these patients should be determined, particularly when scalp-EEG monitoring localizes the epileptogenic zone to one lesion while the other has a known low threshold for epileptogenicity.

Multiple Pathologies

Facing multiple pathologies in patients with drug-resistant epilepsy is often challenging. The most common lesions include cavernous angioma, neurocysticercosis, and malformations of cortical development (MCD).[23]

Multiple lesions could be detected in 12-20% of patients with sporadic cavernous angioma and in more than 50% of familial cases.[64] Despite the potential limiting factors such as the possible formation of new lesions, the development of new epileptogenic zones in pre-existing lesions, and imprecise localization due to proximity of lesions,[23] resection of the responsible epileptogenic focus in patients with drug-resistant epilepsy and multiple cavernous angiomas has been associated with a more favorable outcome compared to medical treatment.[65-68] Thus, a detailed presurgical evaluation of these patients should always be considered.

In areas with a high prevalence of cysticercosis, epilepsy due to multiple lesions caused by neurocysticercosis (NCC) is common, but a sufficient response to medical therapy often obviates the need for further evaluation.[69] However, in the co-existence of HS and NCC, if presurgical evaluation indicates HS as the only epileptogenic zone, a favorable post-operative outcome is expected following ATL, although complete discontinuation of ASMs might not be possible.[70-72]

Based on available evidence, NCC lesions are rarely the epileptogenic zone responsible for refractory seizures, but when there is uncertainty about the presence of an active epileptogenic zone other than HS, a thorough presurgical evaluation including iEEG is

necessary and might lead to dual lesionectomy.[73,74] Currently, individualized decision-making is often used in these patients as the best surgical strategy is yet to be determined.

Patients with MCD frequently experienced poor seizure control on medical therapy. Multiple small and extensive lesions could exist in these patients, which are not always detected by MRI.[75,76] Choosing the best surgical strategy is often challenging and requires a comprehensive presurgical evaluation, including intracranial recording for more diffuse lesions.[77-79] In patients with periventricular nodular heterotopias, localization of epileptogenic focus using iEEG is the main determinant factor for surgical strategy and outcome.[80] The emergence of selective stereotactic ablation techniques has been associated with favorable outcomes. However, bilateral lesions and the presence of concomitant malformations could worsen the outcome.[81-83]

Multiple pathologies, including combinations of different lesions such as FCD, and multiple cavernomas, or HS, FCD and ganglioglioma, have been infrequently reported. The best treatment strategy for these patients is currently individualized and needs to be determined.[84,85]

Conclusion

Despite the various studies on DuP in the literature, decision-making for many patients is still challenging. Precise localization of the SOZ and epileptogenic zone to one or both lesions plays a crucial role in surgery planning. But sometimes it is not possible due to current limiting factors. Facing similar problems in approach to patients with DoP hypothesizes that unifying the terms DuP and DoP might eliminate the existing inconsistencies and provide a simple and more uniform management decisions for both groups of patients. In patients with multiple pathologies, surgical planning is often challenging and requires a comprehensive presurgical evaluation, including intracranial recording, to detect a certain SOZ. However, the possibility of post-surgical seizure recurrence due to the development of new epileptogenic zones can not be overlooked. I believe, despite the existing dilemma, conducting more targeted studies on uniform and classified groups of patients with more acceptable methods could provide a higher success rate in the management of these patients.

Conflict of Interest

The authors declare no conflicts of interest.

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