SHORT COMMUNICATION

Neuropathology of the latin american epilepsy community

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ABSTRACT

Despite ongoing efforts and advancements in research and therapy, many persons with epilepsy remain drug-resistant. Understanding the underlying etiology of epilepsy, whether structural, genetic, infectious, metabolic, immunological or (now) unknown, is critical because it offers crucial information regarding the clinical course. Phenotype, cognitive comorbidities, (new) pharmacological targets, and postsurgical outcomes are all factors to consider. The use of a multimodal strategy, which includes digital slides and multichannel immunofluorescence labeling, can help to improve the results. DNA methylation arrays may aid in the identification of difficult-to-classify lesions, and diagnostic yield of subtle diseases. However, in low-income nations, such approaches are not always available. Even without access to pricey molecular techniques, Latin American researchers can construct automated analysis scripts and machine learning algorithms to boost the diagnostic yield from ordinary Hematoxylin and Eosin stained tissue sections. The Latin American pathology community made a significant contribution to our current state. knowledge of human epilepsies and experimental epilepsy models etiologies To improve the economy, even more, Local centers should use current, multimodal neuropathology techniques, combine multiple levels of expertise, and improve their scientific relationships to maximize the impact of Latin American research. Dedicated teaching courses in Epileptology, such as the Latin American Summer Schools of Epilepsy (LASSE) or International Summer School for Neuropathology and Epilepsy Surgery (INES) addressing young researchers and neurologists, are most successful to promote this endeavor. In this review, we will describe the state of neuropathology in the 21st century and also highlight Latin American researchers' contributions to the current knowledge in the neuropathology of epilepsy.

Key Words: *Neuropathology; Epilepsy; Hippocampal sclerosis; Long-Term Epilepsy-Associated Tumors (LEAT); Mild Malformations of Cortical Development (MMCD)*

INTRODUCTION

The gross neuroanatomy-pathological findings from postmortem analyses of many epilepsy cases were published in 1825 by Camille Bouchet and Jean-Baptiste Cazauvieilh. Wilhelm Sommer concentrated his efforts a few years later. In a set of 90 human hippocampal histopathology results patients suffering from epilepsy, He went into great detail on the typical pattern of Loss of pyramidal neuronal cells in CA1 with gliosis as a side effect Sclerosis (tissue stiffening) has a structural relationship [1]. Following that, Different neuronal cell losses were linked to hippocampal sclerosis. The age of microscopy diagnosis in epilepsy began with patterns in all hippocampus sectors, including CA4. Many disease diagnoses and classification schemes have been created since then, with an emphasis on hippocampal pathology and other pathologies linked to drug-resistant epilepsy. The field of neuropathology has come a long way. even progressed to a clearer understanding of the significance of etiology for managing epileptic patients Pharmacological and surgical treatment techniques, as well as patient care, have been improved as a result of ongoing technological advancements. Even with the third generation of ant seizure medicine and specific surgical treatment techniques, many patients continue to have seizures. If we want to achieve our goals, It is critical to better understand these factors to improve epilepsy treatment [2,3]. Pathology and etiology of diseases at the molecular level. This will finally identify successful diagnostic biomarkers and drug targets in years to come. In the present review, we will evaluate the current state of pathology knowledge of focal, surgically treatable epilepsies, and the advances in technology for the diagnostics and teaching of the neuropathology of epilepsies. It is fair to say that the foundation of contemporary medicine is founded on a thorough grasp of disease etiologies and underlying pathomechanisms, as pioneered by Charite Berlin pathologist Rudolf Virchow and his colleagues in the late 1800s. Many distinct etiologies can cause seizures in the human brain. Epilepsy is caused by a variety of factors that primarily influence the neocortex, such as metabolic and environmental factors. Developmental alterations in a seemingly normal brain region, functional changes in a seemingly normal

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brain region deformities, parasite infections, or neoplasms, all of which impair tissue organization in the end. Especially in epilepsies characterized by a seizure with a localized onset and was subjected to surgical therapy for long-term seizure control, a large number of patients (almost 10,000) revealed a wide range of common and uncommon diseases. It confirms a well-known medical rule: "frequent conditions are frequent," with the ten most common brain lesions accounting for more than half of all cases. More than 80% of all patients whose brains were collected at the European Epilepsy Brain Bank [4]. Microscopy inspection is used to make a histopathology diagnosis. It is frequently difficult, necessitates personal expertise and talents, and should be avoided. For a given ailment, rely on international consensus classification schemes. The World Health Organization has created this for brain cancers. It is now available in its fourth revised edition from the World Health Organization. Version, which includes additional tumor entities and diagnostic tools including testing with a gene panel. There is no such WHO agenda in place. For a high frequency of brain lesions linked to focal epilepsy. As a result, the International League against Epilepsy (ILAE) has established a special task force to fill this void and produce standardized neuropathology classification systems for common brain lesions, such as focal cortical lesions, hippocampal sclerosis, and dysplasia. Hippocampal Sclerosis (HS) is the most common cause of adult focal epilepsy and is characterized by varied patterns of neuronal cell death throughout the human hippocampus's anatomical subfields. The ILAE classification improves on past attempts to classify diseases. a classification of distinct neuronal cell loss patterns, There are three HS subtypes. HS type 1 is characterized by significant neuron loss and gliosis in the CA4 and CA1 areas, as well as varying symptoms. CA3, CA2, and the granule cell layer loss. HS type 2 is less common, with significant loss limited to CA1 (the Sommer sector), and HS type 3 is less common, with the granule cell layer and CA4 subfield (Bratz sector) being primarily damaged [5]. The new classification is significant because it establishes a stronger relationship between pathology and clinical history. As a result, patients with HS 1 and HS 3 in the dominant hemisphere typically have verbal memory problems, HS 3 frequently manifests as dual pathology, and HS 1 is frequently linked to febrile seizures in childhood. Long-Term Epilepsy-Associated Tumors (LEAT) is the second most common epilepsy illness group in adults and children, but they are uncommon in neuro-oncology. They can have a predominantly neuronal dysplastic component (neurocytomas or gangliocytomas), a predominantly glial dysplastic component (astrocytomas or oligodendrogliomas), or, most commonly, a mixture of dysplastic neuronal and neoplastically transformed glial elements (dysembryoplastic neuroepithelial tumors and gangliogliomas). Low-grade tumors with rare malignant transformation are widespread among these different entities. Furthermore, these tumors include satellites or infiltrative patterns that may affect seizure control if they are not detected on presurgical MRI and, as a result, are not eliminated after surgery [5]. Finally, abnormalities of cortical development, the third most prevalent ailment overall and the most common in children, were classified based on cortical disorganization patterns, the presence of aberrant cells, and co-occurrence with other diseases. While Mild Malformations of Cortical Development (MMCD) are characterized by aberrant neuron clusters in layer I or subcortical white matter, FCD type I is characterized by specific cortical layering architectural anomalies. The disorganization is seen in the cortex in FCD type I is either vertical micro columnar pattern (FCD Ia), horizontal/tangential layer disorder (FCD Ib), or a combination of both (FCD Ic). It's still up for debate whether FCD Ib and Ic are real entities with clinical significance, underscoring the urgency of continuous research. Layers II-VI anomalies should be classed as related FCD IIIa, IIIb, IIIc, or IIId when they occur in patients with hippocampal sclerosis, LEAT, vascular abnormalities, or traumatic traumas. The fundamental premise is that concomitant FCD, such as FCD IIIc in Sturge-Weber syndrome and FCD IIId in prenatal encephalomalacia, may contribute to the epileptogenic condition and hence should be included in the resection field. However, further research is needed before this notion may be approved. FCD IIIa is seen in hippocampal sclerosis, while FCD IIIb is found in brain malignancies. Finally, FCD IIa is defined by layer disorganization and nonphosphorylated neurofilament (SMI32) positive dysmorphic neurons, whereas FCD IIb is defined by the presence of vimentin-positive balloon cells in addition to the dysmorphic neurons. Both lesions have been demonstrated to contain brain somatic or double hit germline mutations in mTOR pathway genes, which aid in better understanding the etiology and, in the future, the identification of new therapeutic targets.

For specific disease entities, this method helped to generate consensus, better comprehend the clinical presentation, and predict the postsurgical outcome. The latter was a never-ending challenge, with significant variation between centers. Even in HS, a relatively simple pathology to differentiate, the initial interrater correlation coefficient among numerous skilled pathologists could be as low as 0.1. The standardized grading system increased the agreement to 0.75, resulting in a higher diagnostic yield. The ILAE FCD classification scheme also enhanced inter-center agreement. Pathologists with less experience with epilepsy surgery, on the other hand, will need additional training. Neuropathology training courses are required to close this gap, and they are offered through the International Summer School for Neuropathology and Epilepsy Surgery (INES), which began in Germany in 2013. With offices in Germany, the United States, and China, INES has been training neuropathologists, neurosurgeons, neuroradiologists, epileptologists, and fundamental scientists from all over the world. In Brazil, it occurred three times in 2015, 2017, and 2019. Continuous medical education in epileptology will be an important next step towards standardization. The ILAE recently launched its Academy (www.ilae-academy.org), a web-based organized education program. For the most frequent epilepsies, a self-paced, tutors case-based eLearning curriculum is supported with histology tutorials of common brain lesions, and augmented by face-to-face courses such as INES, which will be in its 11th edition in 2021. In addition, the Latin American Summer School has covered neuropathology in multiple editions [6].

These actions, in conjunction with the ILAE Academy, will have a substantial impact on the epileptology educational landscape and eliminate therapy gaps for our patients. The ILAE published guidelines for the optimal tissue processing and basic staining methods to improve neuropathology diagnosis in drug-resistant epilepsies as part of the same neuropathology standardization initiative. Both efforts are critical because they set a minimum quality standard for diagnosis and data sharing between different locations. Whole slide imaging was established more than 20 years ago and is now widely utilized for diagnoses and research in many industrialized countries. Although bubbles, wrinkles, and folds are a big worry when utilizing WSI, i.e., the focus cannot be altered after the scanning, and the first adaption of imaging parameters takes time, digital microscopy offers a unique experience and new options for pathologists. Digital pathology reduces

the time it takes to transfer primary data for microscope evaluation and long-distance consultation with other specialists, while glass slides can shatter, get misplaced, and fade over time. Regardless of data storage beyond terabytes, big WSI series data security and confidentiality remain an issue, as the European Reference Network EpiCare has already proposed. To address these concerns, there are digital neuropathology recommendations. However, in middle and low-income nations, pricey digital slide scanners are difficult to come by and maintain, limiting their availability. Nonetheless, some Brazilian colleges now have digitization capabilities. Neuropathology departments will transition from ever-growing physical archives for microscopic brain specimens to huge digital servers as a result of digitalization. Universidad de Sao Paulo (USP), Universidad de Campinas (Unicamp), and Universidad Federal de Sao Paulo (UNIFESP) have already reached an agreement with Google for limitless digital storage. These agreements aid in the reduction of local costs and the promotion of collaboration between national and international centers. However, with long-term re-identification and retrieval of clinical information, these systems must always consider ethical considerations of patient confidentiality.

Digital pathology was introduced into the epileptology arena over a decade ago to test the diagnostic agreement of the ILAE consensus categorization of FCD and found a high interobserver agreement among 30 neuropathologists from various nations and levels of experience. In addition, digital slides were widely used in research investigations to examine microscopic abnormalities detected in the epileptogenic zone. Studies used the technique to assess abnormal astrogliosis, astrocytic coupling, and purinergic signaling in neuromodulators neurons of the caudal medulla in individuals with sudden unexpected death from epilepsy. In cortical malformations such as FCD IIb and Tuberous Sclerosis (TSC), digital imaging confirmed the relationship between decreased myelination, vimentin-positive balloon cells, and phosphorylated S6 ribosomal protein-positive dysmorphic neurons. The Region of Interest (ROI) for semi-/quantitative analysis in digital slides can be as large as the complete specimen, compared to the previously employed practice of generating small and random ROI at 10x objective magnification with analog photomicroscopes.

Stacks of digital slides can also be opened and processed at the same time to superimpose sequential sections stained with distinct staining's, such as immunohistochemistry. The use of several fluorescence-coupled antibodies in the same section enables for localization of the antibodies in a single cell type of interest and the computation of signal overlap (Menders' overlap coefficient) within a single cell or ROI. Even if no relevant antibody exists to identify the protein of interest, techniques like RNAscope can be used in conjunction with immunofluorescence in formalin-fixed, paraffin- embedded samples to allow numerous detections in the same tissue. Multichannel fluorescence can help to identify regions in tissue samples from a given patient with a higher degree of abnormal cells, increasing the chances of finding genetic and epigenetic mutations in the pathology of interest, such as identifying a frameshift insertion in the DEPDC5 gene of a bottom-of-sulcus FCD IIa case. Multichannel fluorescence and specific cortical layer markers can also help detect modest cortical abnormalities that aren't connected with aberrant cell types. Finally, multichannel fluorescence can help with neoplasia diagnosis and treatment by allowing researchers to correlate mutations of interest, cell markers, and the proliferation index all on the same slide. In one simple example, a combination ki67/cytokeratin index outperformed the ki67 proliferation index alone in predicting breast cancer. As previously stated, great attention should be given when purchasing a slide scanner, as not all scanning microscopes have the capability of scanning fluorescent dyes. Matching WSI with in vivo or ex vivo MRI images is also a powerful method. MRI-histology matches may be easily established and corrected for any distortion produced by tissue processing using specialized registration pipelines. In this regard, ex vivo 7 T T2 signal, fractional anisotropy, and mean diffusivity in white matter/perturbed areas coincided with histological markers for myelination and astrocytic response in three TSC individuals. Neuron density within the tuber, on the other hand, was linked to mean diffusivity. Increased T2 signal and increased balloon cell/decreased myelination were reported to have a similar relationship in an FCD IIb research. With 7 T tractography, different HS types showed unique fiber tract organization in another investigation.

Big data acquisition in neurology can be the result of evaluating enormous quantities of clinical data from hundreds of patients or simply measuring the methylation status of a single patient's DNA with 850.000 single nucleotides collected in one array. Working with such a large amount of data necessitates meticulous standardization, especially when samples are collected from several research institutions. The ILAE Big Data Task Force has released an early study that demonstrates the necessity for an organized approach to big data in epilepsy and recommends particular standards for each category of data. The OMICS techniques, which aim to analyze proteins (proteomics), genes (genomics), gene transcription (transcriptomics), and gene regulation (epigenomes), among other things, have shown promising prospects for comprehending a complicated disease like epilepsy. When compared to age-matched autopsy controls in temporal lobe epilepsy, a proteomic analysis of hippocampi from drug-resistant patients revealed an increase in oxidative stress, axonal rearrangement, and energy metabolism proteins. The direct relationship between the differently expressed proteins and 20 other cell proteins suggests that the epileptogenic zone can alter numerous metabolic networks. Granule cell dispersion was connected to multiple proteins involved in axon guidance, cytoskeleton control, and synaptic remodeling, and was first linked to reduced reel in expression and increased reel in gene methylation. High spiking regions displayed a reduced astroglial reaction, an increase in many proteins associated with vascularization, and an increase in phosphoproteins connected to neuron cytoskeleton when compared to low spiking frequency cortical samples. Finally, metabolic variations in glutamate, glutamine, and n-acetyl-aspartate between HS1 and HS2 were discovered in intact hippocampi . In the field of epileptology, epigenetic studies had come to our attention. DNA methylation, histone acetylation, and microRNAs are major epigenetic alterations that are altering the landscape of various epilepsy pathological types. These changes may also pave the way for new treatments for drug-resistant epilepsies. While there is a widely accepted epigenetic profiling for brain cancers, which may be combined with the WHO genotype-phenotype categorization scheme in the future, our understanding of the genetic basis of cortical abnormalities is still in its infancy. While FCD IIb and HME demonstrated a lower prevalence of brain somatic mutations or variants of uncertain relevance, TSC patients with TSC1 or TSC2 germline mutations account for more than 80% of TSC patients. Recent research has proven the importance of genetic testing in the mTOR pathway in FCD II and HME, particularly in glial cells and major excitatory neurons, with mutations found in 63 percent of the patients analyzed. The resemblance of such disorders at the histology level is very high, and it might be difficult for less experienced pathologists to separate them, as will be explained in the next session.

The missing link explaining why patients with no mutation present with the aberrant phenotype could be epigenetic silencing or activation of gene transcripts. Differential methylation signatures able to distinguish temporal lobe epilepsy, FCD Ia, FCD IIa, and FCD IIb were discovered using next-generation sequencing of whole-genome DNA methylation. Differential methylation of FOXO6 separates controls from FCD I and II, while DEPDC5 methylation separated FCD II from TLE among the detected variations. As demonstrated by the previously described classifier of 82 brain tumor types based solely on their differential DNA methylation profiles, these pattern discrepancies have significant promise for the classification of these illnesses. In the realm of epileptology, large multicentric studies are needed to define a precise genotype-phenotype correlation and its link to variances in clinical presentation and post-surgical prognosis. The combination of WSI, huge genetic/epigenetic/proteomic data and machine learning algorithms to classify and study anomalies in the epileptogenic zone will represent the new standard for patient treatment as pathology transitions from analog to digital [7].

CONCLUSION

Regardless of financial constraints, the Latin American pathology community must try to reach this level, to contribute new information as well. While some techniques will be more difficult to combine due to financial constraints, machine learning algorithms are generally free and provide a great opportunity for new research areas, particularly the integration of pathological, clinical, electrographic, and radiological data from tropical etiologies associated with epilepsy (e.g., Zika virus and neurocysticercosis). Collaboration with significant European and North American centers will also help us maintain our momentum.

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