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ETIOLOGY AND DIAGNOSIS CHALLENGES OF EPILEPSY

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Abstract:

The purpose of this review was to evaluate the challenges facing neurologist in the diagnosis of epilepsy, therefore, discussion of diagnostic procedures was demonstrated in this study, the second aim of this paper was to review the etiological factors associated with epilepsy. Detailed search and review of the literature was conducted using electronic databases, MEDLINE, EMBASE, and SCISEARCH; up to end of 2019, for studies reporting data on diagnosis and causes of epilepsy in all pollutions worldwide. Restriction to studies published in English and with human subjects was applied in our search strategies. It is evident that epilepsy is a complex and heterogeneous disorder with a long list of risk factors. We evaluated epilepsy etiologies and highlighted the primary risk-defining specifications as far as possible (injury severity, low grade tumors especially of temporal localization, early onset, genetic origin), which may promote prompt identification of a suitable target population (individuals at risk of establishing epilepsy). Variable significance of private etiologies (stroke, perinatal injury, infections in low earnings countries and existence of cofactors (other diseases or clinical symptoms) might cause region-specific epilepsy frequencies. Epilepsy is a medical diagnosis that is frequently based on medical history alone as healthcare providers hardly ever personally observe the patient's seizure activity. EEG is the most important diagnostic tool that may help in diagnosis, seizure category, and monitoring response to treatment.

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INTRODUCTION:

Epilepsy is a major neurological disorder, the signs of which are controllable and preventable to some extent and which has deep scientific, psycho-- socio-- market and financial ramifications that differ across various areas of the world [1,2,3], and are connected with varied incidence, occurrence and death [1,2,3]. Epilepsy is defined as a condition characterized by frequent (2 or more) epileptic seizures, unprovoked by any instant determined cause [2,3]. Several seizures taking place in a 24-hour period or an episode of status epilepticus (SE) are considered a single occasion. A seizure is the symptom of an abnormal, hypersynchronous discharge of a population of cortical neurons. This discharge might produce subjective signs or goal signs, where case it is a clinical seizure, or it may be apparent only on an electroencephalogram (EEG), where case it is an electrographic (or subclinical) seizure. Around 50 million individuals worldwide have epilepsy and approximately 5% of the general population experience at least one seizure, leaving out febrile seizures, at a long time in their lives [4,5,6]. The occurrence of epilepsy is around 0.5-1%, and its total yearly incidence varieties from 50-70 cases per 100,000 in industrialized nations and up to 190 per 100,000 in developing nations [7,8]. Around 80% of people with epilepsy reside in developing nations [9,10,11]. The high occurrence in establishing countries is attributed to poor obstetric services and the greater risk of intracranial infections and head injuries [12]. Moreover, in these nations 80-90% of epileptic patients have problems in accessing treatment [9,10]. This treatment gap has actually been generally ascribed to inefficient and unevenly dispersed health-care systems, expense of treatment, cultural beliefs, and unavailability of antiepileptic drugs [10,11]. The medical diagnosis of epilepsy in establishing countries is an uphill struggle. Video-electroencephalogram (EEG) and ambulatory long-term EEG monitoring provide a fantastic assistance for the differential medical diagnosis of epilepsy and other paroxysmal events, but in lots of locations of establishing countries, especially rural areas, these diagnostic strategies are not offered. Due to absence of these facilities, high rates of misdiagnosis are likely in these countries. The majority of studies recommend there is a slightly higher incidence of epilepsy in males then women [5,6]. The discovery of the EEG in the 1920s helped in correlating the neuronal activities to the behavioral conditions [13]. Currently, advances in medical imaging methods, as well as in genetics, have led to better and new treatment methods [14,15]. The purpose of this review was to evaluate the challenges facing neurologist in the diagnosis of epilepsy, therefore, discussion of diagnostic procedures was demonstrated in this study, the second aim of this paper was to review the etiological factors associated with epilepsy.

METHODOLOGY:

Detailed search and review of the literature was conducted using electronic databases, MEDLINE, EMBASE, and SCISEARCH; to the end of 2019, for studies reporting data on diagnosis and causes of epilepsy in all pollutions worldwide. Restriction to studies published in English and with human subjects was applied in our search strategies.

RESULTS:

- **Etiological factors associated with epilepsy:**

Occurrence studies offer a better understanding of the etiology and natural history of epilepsy. From the readily available literature, causes appear to be controlled are head injury, birth trauma, asphyxia, cerebrovascular disease, and intracranial infections (neurocysticercosis or meningoencephalitis). Hereditary factors have a strong association with distinctive epilepsy.

Traumatic epilepsy:

Brain injury (BI) is among the most crucial risk factors for epilepsy. In a large population-based research study conducted in Rochester (MN, USA), head trauma was identified as the cause of epilepsy in 6% of the population [16]. Generally, as much as 20% of all symptomatic epilepsy cases are credited to brain injury [17]. The epilepsy risk depends carefully on the degree of injury. Cases with moderate brain injury (MBI), defined as a direct injury versus the head and characterized by modifications in brain function, that is, loss of awareness, amnesia, confusion and focal momentary neurological deficit, ought to be identified from extreme brain injury (SBI), which presents structural injuries including brain contusion or intracranial hemorrhage. In MBI, the risk of epilepsy was two times as high as in individuals without BI (relative risk [RR]: 2.22; 95% CI: 2.07- 2.38), whereas it was sevenfold higher amongst cases with SBI (RR: 7.40; 95% CI: 6.16 - 8.89) [18]. Head injury is the primary cause of epilepsy and account for 5% epilepsy and 20% of symptomatic epilepsy [19].

CNS Infections

The Commission on Tropical Disease of the International League Against Epilepsy noted several diseases as reasons for epilepsy, consisting of malaria, tuberculosis, schistosomiasis, obtained immunodeficiency syndrome, and cysticercosis [20]. An association between neurocysticercosis and epilepsy is discovered in different research studies in Africa and Latin America the results on the relation between neurocysticercosis and epilepsy in Asia is varied considerably [21]. Neurocysticercosis is most likely a crucial reason for seizures and epilepsy in areas with a high frequency of Taeniasolium infection in human beings [22,23].

Genetic Factors

Some studies show that there is no association of hereditary factors with epilepsy [24,25,26]. Nevertheless, family history and mainly hereditary factors is linked to epilepsy in numerous studies [27,28]. The most common human hereditary epilepsies display a complex pattern of inheritance and the associations with genes are mostly unidentified. Pathogenic alterations or anomaly in genes and structural problems in chromosomes (deletions, insertions) are accountable for a range of epilepsies [19]. Although numerous genes and their corresponding anomalies have been recognized, these represent only a little proportion of idiopathic epilepsy and other rarer epilepsy kinds, and specific genetic influences stay to be determined in the majority of cases. In general, research studies have shown a high concurrence rate of epilepsy among monozygotic compared with dizygotic twins (62 vs 18%) [29], along with a fivefold higher epilepsy risk in close family members of epilepsy cases [30].

Multiple sclerosis:

It is uncertain whether a relationship in between epilepsy and numerous sclerosis (MS) is either symptomatic or coincidental. Epileptic seizures can be the first observable sign in 10% of cases [31] and could be of significance considering that numerous MS lesions, even when examined by MRI, remain quiet [32]. Epilepsy rates are especially high in some studies in the MS population. One research study found a threefold higher rate or significantly greater ageadjusted occurrence [33,34]. Seizures are particularly partial (basic and complex) and occur in a higher proportion in patients with MS than that observed in a basic epilepsy population (50 vs 30%) [34,35]. Proof suggests that cortical and subcortical demyelinating lesions are themselves irritative foci [34]. MRI research studies have actually shown a greater frequency of MS lesions that extend into the cortex when epilepsy was present. Frontal atrophy in epilepsy cases may also have a function in epileptogenesis [34,35].

Brain tumors as cause of epilepsy:

Brain tumors, malignant or benign, are a common reason for epilepsy and yield an epilepsy incidence of nearly 30% [37]. On the other hand, practically 4% of epilepsy patients have brain tumors [38]. The risk for establishing epilepsy is higher amongst grownups than children and this epilepsy risk depends upon lots of factors consisting of tumor type, tumor grade or location, existence of cerebral hemispheric dysfunction or insufficient tumor resection [37,38,39]. The factors that are mostly related to adult epilepsy include melanoma, hemorrhagic sores, numerous metastases and gradually growing primary tumors. Factors among children include gangliogliomas, low grade astrocytomas, dysembryoplastic neuroepithelial tumor and oligodendrogliomas [39]. WHO gradeI tumors (such as gangliogliomas and pilocytic astrocytomas) might be the most substantial epilepsy predictor since they are most frequently seen (70% of cases) amongst patients with primary brain tumor and drug-resistant epilepsy [40].

A study revealed that the frequency of epilepsy differed from 22 - 37% amongst those with high grade and 50 - 90% amongst low grade primary brain tumors [41]. Low grade tumors are more likely to be related to epilepsy because their sluggish development might permit more time for epileptogenesis to develop, whereas high grade tumors (e.g., glioblastomas) are malignant, grow rapidly and most likely destroy close-by neurons instead of promoting them. In low grade tumors, intractable epilepsy could be due to the tendency to develop secondary epileptogenic foci that appear to be associated with temporal place, young age and duration of disease [42].

Stroke & epilepsy:

Stroke is a significant risk factor for epilepsies. It may describe a 3rd of those that take place in the senior population and there is most likely a relationship in between epilepsy and stroke risk in later life [43,44]. In a number of big and properly designed potential research studies, 2- 4% of stroke cases were revealed to experience epilepsy throughout their life time. These rates are much higher in smaller sized (e.g., 6 - 9%) or retrospective studies (e.g., 39% over 30 months) [45]. These rates also differ from population to population and in between various periods of follow-up, for example it was 3.8% in a UK population over 5 years. The risk of epilepsy related to stroke has actually been shown to be 3.4% in an US population over 5.5 years, 2.5% over 9 months in a Scandinavian population, 32% (of those who had early start of seizures) over 26 months in Australian population [45]. The medical diagnosis of a post-stroke seizure is difficult because seizure can be identified by unfavorable motor symptoms and might look like short-term ischemic attacks. Risk factors for epilepsy or early seizure are dependent on stroke subtype, stroke place and stroke disability. Hemorrhagic stroke is often reported in patients affected with early seizures in current associates [46], while it was also associated with post-stroke epilepsy (PSE) in older works [47]. Atherothrombotic and cardioembolic stroke types are together responsible for practically 74% of cases [46]. (**Figure1**) summarize the Etiological factors associated with epilepsy in relation to age.

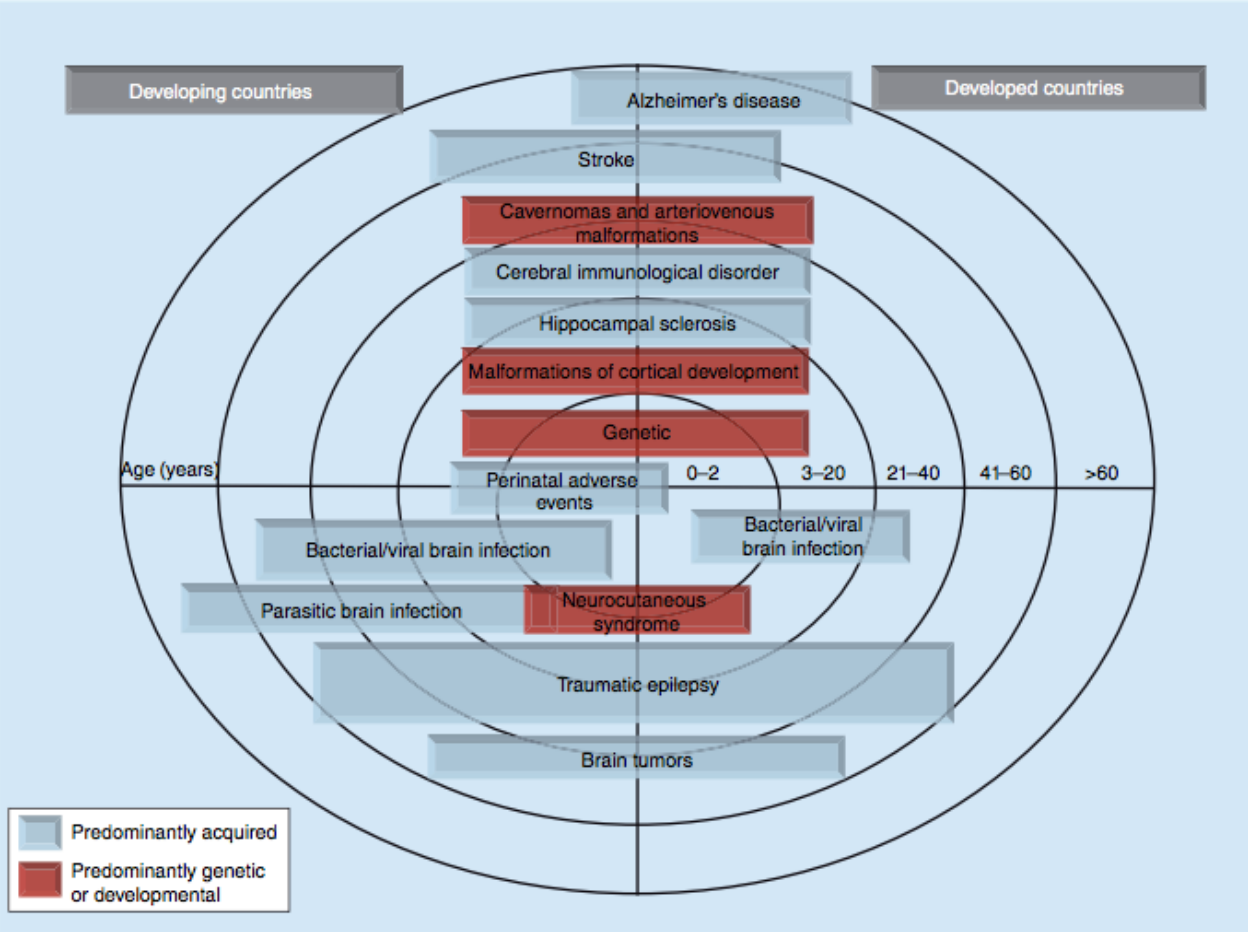

Figure1: Causes of epilepsy

○ **Diagnosis challenges of epilepsy:**

The incorrect medical diagnosis of epilepsy is regrettably common. Of patients identified with epilepsy who are seen at epilepsy centers, 20% to 30% are discovered to have been misdiagnosed [1,2,3]. This portion is remarkably consistent across countries, centers, and continents. Psychogenic nonepileptic attacks (PNEAs) are by far the most common condition found at recommendation epilepsy centers and epilepsy tracking units, though syncope might be more typical in a general neurology practice setting. Other paroxysmal conditions can also periodically be misdiagnosed as epilepsy. As is true of other chronic conditions (e.g., numerous sclerosis), when a wrong medical diagnosis of epilepsy has actually been given, it is easily perpetuated without being questioned, which explains the normal diagnostic delay and its repercussions [12,15]. Amazingly, in spite of the ability to make a diagnosis of epilepsy (and its primary imitate PNEA) with near certainty, the delay in diagnosis stays long at about 7 to 10 years [19,20]. Neuroimaging studies play an integral part of seizure and epilepsy assessment for the determination of the practical and structural etiology of seizures. Existing basic neuro-radiological imaging consists of 3T brain MRI with coronal or oblique-coronal images using T1-weighted and T2-weighted series in addition to fluid-attenuated inversion-recovery (FLAIR). 1.5 T brain MRI can also localize seizure foci, it is less sensitive than greater field 3T MRI [48]. The sensitivity of MRI for intractable epilepsy remains in basic 82-86% [49,50]. Considering that several sores might cause seizures, MRI is often a beginning point for differentiation. These lesions consist of mesial temporal sclerosis (MTS), genetic brain abnormalities both syndromic and migrational like Sturge Weber, tumors, infections and vascular malformations such as spacious malformations and arteriovenous malformations. A traditional case of MTS will display hippocampal atrophy with abnormal T2 and FLAIR signal in the hippocampus (**Figures 2),** as well as decreased FDG uptake in PET scan (**Figure 2**).

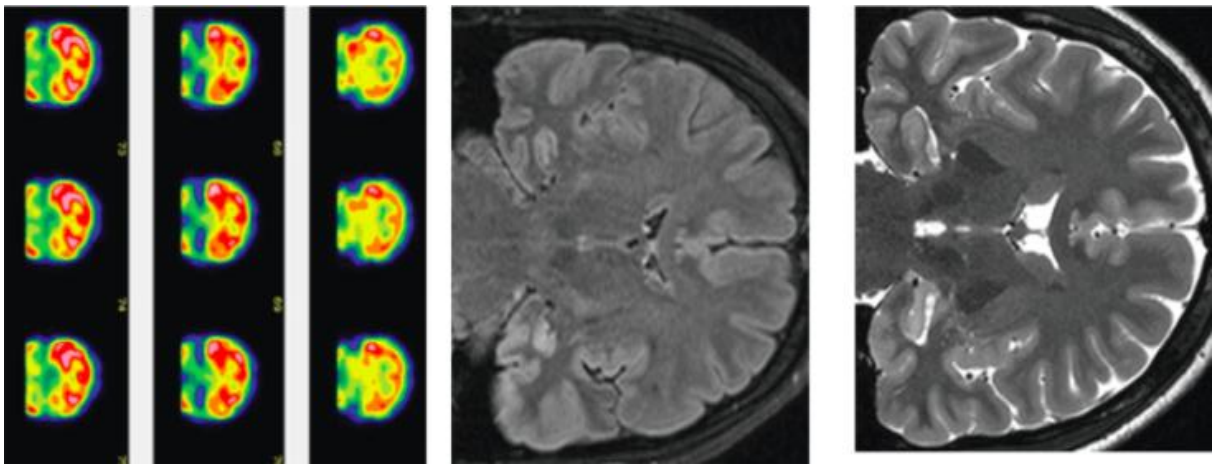

Figure 2: Mesial Temporal Sclerosis in MRI and PET Studies: The image on the Right is a coronal T2-weighted MRI exhibiting a smaller and slightly bright left hippocampus

Roles of Electroencephalography in diagnosis of epilepsy:

The EEG is the most typically performed diagnostic study in people with epilepsy. The first EEG performed on an individual was recorded by Hans Berger in 1924, and the importance of EEG in the assessment of patients with epilepsy was confirmed by numerous investigators in the 1930s. The EEG has actually enhanced our understanding of the pathophysiology of seizures and has actually been an invaluable diagnostic tool in the assessment and treatment of seizure conditions [51,52]. Early observations worrying using EEG in epilepsy verified the basic tenets outlined by J. Hughlings Jackson and his coworkers in the 19th century relating to cortical excitability and hypersynchrony in focal seizures [53]. The routine awake and asleep EEG recording may be gotten on an outpatient or inpatient basis and consists of triggering procedures, such as eye opening and eye closure, hyperventilation, and photic stimulation. The significance of sleep deprivation and the efficiency of the EEG recording during sleep in patients with epilepsy have actually been stressed [54]. In chosen patients, the epileptiform discharges might only be present throughout the sleep EEG recording. The AAN recommends EEG in diagnosing epilepsy in adults and children, with inclusion of photic stimulation, hyperventilation, and sleep deprivation in grownups as part of the procedure [51]. EEG studies may reveal interictal epileptiform abnormalities. Repetitive EEGs may be of diagnostic importance and might evaluate the patient's action to therapy. Epileptiform problems usually look like spikes, sharp waves, or spike-wave discharges that stand out from the typical background activity and suggest an increased seizure tendency. The spike discharges are predominantly negative transients with steep ascending and descending limbs and a period of 20 ms to 70 ms. A sharp wave is a more comprehensive potential with a period of 70 ms to 200 ms. The epileptiform discharges should stand out from the typical background activity, involve more than one scalp electrode, and have a physiologic field, and a voltage gradient need to exist. Knowledge about the patient's age, coexistent medication utilizes, state of awareness, and medical history are had to appropriately translate the EEG research study. The conceptual age of the patient is very important for neonatal recordings. An epileptiform pattern seen on EEG after a novice seizure typically anticipates recurrence of seizures based upon research studies in both adults and children, with reoccurrence rates that range from 30% to 70% in the very first year [55]. For that reason, when the EEG reveals an epileptiform discharge after a single seizure, treatment may be considered even prior to a medical diagnosis of epilepsy is developed. The medical applications of EEG include diagnosis of epilepsy, selection of AED therapy, assessment of reaction to treatment, decision of candidateship for drug withdrawal, and surgical localization. Level of sensitivity and specificity. The level of sensitivity of a single EEG study to tape an epileptiform problem may be 50% or less in individuals with epilepsy [54].

Electrocorticography:

Intraoperative electrocorticography (ECoG) was presented several years ago to identify the level of resection, mainly in partial temporal lobe resections. If epileptiform activity might still be tape-recorded from the remaining tissue, the resection could be bigger. As for intraoperative electrical stimulation, ECoG has rigorous time restrictions and is usually restricted to less than 30 minutes of recording. The significance of resecting areas with interictal epileptiform activity is not well studied, and the zone from which interictal epileptiform activity can be recorded is typically far larger than the real seizure start zone. ECoG probably does not contribute much to standardized treatments like an anterior temporal lobe resection, but might be valuable in determining the level of resection in

more diffuse pathologies such as focal cortical dysplasia [56]. Some ECoG findings that were thought to be specific to focal cortical dysplasia were gotten in other pathologies [57] and, therefore, appear not to be as particular as formerly thought [56,57].

CONCLUSION:

It is evident that epilepsy is a complex and heterogeneous disorder with a long list of risk factors. We evaluated epilepsy etiologies and highlighted the primary risk-defining specifications as far as possible (injury severity, low grade tumors especially of temporal localization, early onset, genetic origin), which may promote prompt identification of a suitable target population (individuals at risk of establishing epilepsy). Variable significance of private etiologies (stroke, perinatal injury, infections in low earnings countries and existence of cofactors (other diseases or clinical symptoms) might cause region-specific epilepsy frequencies. Epilepsy is a medical diagnosis that is frequently based on medical history alone as healthcare providers hardly ever personally observe the patient's seizure activity. EEG is the most important diagnostic tool that may help in diagnosis, seizure category, and monitoring response to treatment.

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