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Analysis of the aetiology of epilepsy in 3,216 adult patients attending a tertiary referral center enabled by an electronic patient record

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\textbf{ABSTRACT}

\textbf{Purpose:} The aim of this study was to review the causes of the epilepsies in our institution, an adult tertiary referral center for neurology and neurosurgery in Dublin, Ireland. Data was obtained from a bespoke epilepsy electronic patient record (EPR).

\textbf{Methods:} Predetermined search parameters of well-established broad categories of epilepsy aetiology were used to identify patients with a diagnosis of epilepsy attending Beaumont Hospital, Dublin. There were 3216 patients that met the inclusion criteria for this study. We included living patients with epilepsy attending our institution. We then excluded patients with a diagnosis of pure non-epileptic attack disorder and patients found to have idiopathic generalised epilepsy (IGE) (n = 382) from our final cohort. We excluded IGE due to the complex polygenic basis underlying this patient group.

\textbf{Results:} An aetiology was identified in 54.3 \% (n = 1747) of the total number of patients studied. Of the symptomatic epilepsies, 41.08 \% (n = 1321) were acquired and 13.3 \% (n = 426) were predominantly of genetic / developmental aetiology. The most common causes of the acquired epilepsies were hippocampal sclerosis (n = 380; 28.75 \%), cerebral tumor (n = 279; 21.06 \%), traumatic brain injury (n = 248; 18.77 \%), stroke and cerebrovascular disease (n = 151; 11.43 \%) and perinatal causes (n = 138; 10.45 \%). The leading causes in the genetic / developmental category included cavernous haemangiomas (n = 62, 22.22 \%), arteriovenous malformations (n = 59; 21.15 \%) and cortical dysplasia (n = 55; 19.71 \%). The aetiology of a patient’s epilepsy was undetermined in 45.68 \% (n = 1469) of individuals.

\textbf{Conclusion:} This study emphasizes the clinical utility of the ILAE’s 2017 revised classification of the epilepsies and highlights the evolving dynamic nature of attributing causality in epilepsy. This is the largest single centre analysis of the aetiology of the epilepsies described in the literature. It is also the first large scale study examining aetiology utilising a bespoke electronic patient record in epilepsy.

1. Introduction

Lennox historically compared the array of exposures and causes of seizure genesis to ‘the river of epilepsy’ [1]. There are few large-scale studies examining aetiology in epilepsy across populations. The results from existing studies indicate that there are considerable disparities between the aetiologies of the epilepsies globally. The aetiology of epilepsy in an individual is likely shaped by a complex interplay between genetic makeup, neuronal remodelling in response to prior and existing brain disease, and other epigenetic factors. There is a higher rate of epilepsy attributed to perinatal injuries in Sub-Saharan Africa, where significant neonatal mortality and morbidity remains due to inequalities in access to health resources and deficiencies in obstetric care [2]. Conversely, aetiologies related to older age and increased life expectancy, such as neurodegenerative disorders and cerebrovascular disease, are more evident in Scandinavia and China and other developed countries [2,3]. Attributing causality in epilepsy care can be a challenging process. The determination of aetiology can be influenced by access to appropriate modern diagnostic resources and expertise. It is estimated that approximately 30 \% of patients with symptomatic epilepsies have causes attributed to a previous brain insult such as encephalitis, trauma, stroke, and prior prolonged acute symptomatic

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to represent epilepsy related to complex polygenic aetiology. There is no clear division of epilepsies in our institution, we decided to exclude any patients found to have a diagnosis of non-epileptic attack disorder and epilepsy were also included. Since the objective of the study was to derive a diagnosis of epilepsy. A total of 3216 records were deemed suitable for inclusion, and these were systematically reviewed by the first author (SD).

2. Materials and methods

2.1. Study design

This study was carried out at Beaumont Hospital, Dublin, a tertiary referral centre for adult neurology and neurosurgery, and the epilepsy surgery center for Ireland. We conducted a cross-sectional analysis of a prospectively maintained epilepsy EPR between January 2018 to November 2018 (Fig. 1).

The search criteria presented to our research engineers to yield the initial patient population included 'living patients' and 'patients with a diagnosis of epilepsy'. Further manual analysis of the aforementioned initial patient cohort identified patients who were deceased patients (n = 12), individuals with an exclusive diagnosis of non-epileptic attack disorder (n = 17) and those without evidence of a diagnosis of epilepsy (n = 73) were excluded. Patients with dual diagnoses of non-epileptic attack disorder and epilepsy were also included. Since the objective of this study was to delineate specific symptomatic aetiologies of the epilepsies in our institution, we decided to exclude any patients found to have a diagnosis of idiopathic generalised epilepsy from our final patient cohort on the basis that this cohort of patients are now thought to represent epilepsy related to complex polygenic aetiology. There is an inherent selection bias attached to the search parameters utilised to extract data from the electronic patient record. The number of patients excluded with a diagnosis of idiopathic generalised epilepsy are not representative of the overall number of patients with this diagnosis attending our hospital. The generalized epilepsies denote an epilepsy type in accordance with the ILAE but do not represent an etiological category [6]. The idiopathic generalized epilepsies were defined by an absence of cerebral lesions and characteristic bilaterally synchronous 3 Hz or greater spike-wave EEG abnormality in an appropriate clinical context [10]. The symptomatic generalized epilepsy group were defined according to the ILAE definition stipulated in the 2017 position paper [6]. Patients were excluded from analysis if there was insufficient clinical data populated within a patient’s EPR on which to be able to derive a diagnosis of epilepsy. A total of 3216 records were deemed suitable for inclusion, and these were systematically reviewed by the first author (SD).

2.2. Diagnosis and definitions

We separated the overall aetiologies in accordance with the updated 2017 guidelines of the International League Against Epilepsies [6,11]. The symptomatic epilepsies were divided into (i) acquired and (ii) genetic or developmental aetiologies to better delineate the exact aetiological basis and to facilitate data extraction in accordance with the classification structure setup in our EPR software. The acquired aetologies include causes such as hippocampal sclerosis, perinatal and infantile insults, brain trauma, tumors, infections, neurodegenerative conditions, and immunologic conditions. The genetic and developmental categories respectively include chromosomal disorders, developmental anomalies such as cortical dysplasia and schizencephaly, single gene disorders, neurocutaneous disorders, the progressive myoclonic epilepsies, and childhood eponymous syndromes including West and Lennox-Gastaut syndromes. The unknown category encompasses the epilepsies for which no cause has been identified.

Research engineers (RP, SO'D) at the Royal College of Surgeons of Ireland extracted data from the EPR for those patients meeting the inclusion criteria attending Beaumont Hospital. The search parameters used to extract the initial patient cohort were selected in accordance with the existing structure of the EPR. The following search criteria were selected as broad filters: 'neurocutaneous', 'mesial temporal sclerosis', 'perinatal injury', ‘fetile convulsions’, ‘traumatic brain injury’, ‘encephalitis’, ‘meningitis’, ‘other CNS infections’, ‘vascular malformations’, ‘stroke’, ‘cortical developmental malformation’, ‘chromosomal abnormality’, ‘brain tumour’, ‘genetic’ and ‘family history’. Each of these respective aetiologies can be expanded in further detail in accordance with the EPR dropdown menus (Fig. 2).

The integrated nature of the EPR facilitates interrogation of large volumes of data previously inputted into the database. A literature search was conducted to identify similar large-scale studies conducted worldwide examining aetiology in epilepsy to date as outlined in Table 5. The following search terms were entered into Google Scholar and PubMed; ‘aetiology’, ‘etiology’, ‘causation’, ‘epilepsy’, ‘seizures’, ‘global’, ‘worldwide’ and reviewed by the first author.

3. Results

Clinical characteristics, EEG findings, neuroimaging and laboratory data were examined for 3216 patients, and aetiology was matched with broad syndromic classification. The acquired symptomatic epilepsies accounted for 40.9 % (n = 1321) of the overall aetiologies of patients attending our hospital (Table 1). The epilepsies in this category exclude genetic or developmental causes. Of these, the most common aetiologies included: hippocampal sclerosis (n = 380), cerebral tumor (n = 279), traumatic brain injury (n = 248), cerebrovascular disorders (n = 151), and perinatal causes (n = 138). The breakdown of results yielded from analysis of the acquired epilepsies are reflective of our centre’s role as a national referral centre for neurology and neurosurgery. The tumor-related epilepsies account for 21 % of the acquired epilepsies within our patient cohort (Table 2). Our results reveal astrocytomas to be the most common type of cerebral tumour (n = 79), accounting for...
### Aetiology

| **Family History** | Possible | | Brother, paternal first cousin and uncle |
| **Genetic** | Definite | |
| **Perinatal Injury** | Possible | |
| **Fever** | No | |
| **Convulsions** | No | |
| **Meningitis** | No | |
| **Encephalitis** | No | |
| **Other CNS Infection** | | |
| **Traumatic Brain Injury** | Possible | |
| **Mesial Temporal Sclerosis** | | |
| **Brain Tumour** | Astrocytoma Grade 2 | | surgery 2006 |
| **Vascular Malformation** | | |
| **Stroke** | | |
| **Cortical Developmental Malformation** | | |
| **Neurocutaneous Syndrome** | Other | | neurocutaneous |
| **Hydrocephalus** | | |
| **Chromosomal Abnormality** | No | | details.... |
| **Neurodegenerative Disease** | Possible | | details.... |
| **Unknown** | | |
| **Other** | | |
| **Acute Symptomatic** | | |

Fig. 2. EPR Aetiology user interface [for color print].

![Graph showing the overall breakdown of the most common aetiologies of the epilepsies.](image)

Fig. 3. Overall breakdown of the most common aetiologies of the epilepsies [for color print].
27 % of the overall tumor category. The other leading tumor causes include oligodendrogliomas (n = 60), meningiomas (n = 37), and dysembryoblastic neuroepithelial tumors (DNETs) (n = 28). Cerebral infections account for a sizeable proportion of the acquired epilepsies (n = 61). Cumulatively cerebral infections constitute the epilepsies caused by encephalitis (n = 25), meningitis (n = 15), abscess (n = 6), and infections which were not specified (n = 12) and the less frequently encountered types of cerebral infections such as subacute sclerosing panencephalitis, rubella; neurocysticercosis and cerebral tuberculoma. Over 13 % (n = 425) of the patient cohort had a predominant genetic or developmental symptomatic epilepsy. Within this group, major causes included developmental anomalies of cerebral structure (n = 279) and tuberous sclerosis (n = 33) (Table 3). The notable leading causes of epilepsy within the spectrum of disorders of cerebral structure include cavernous haemangiomas (n = 62) and arteriovenous malformations (n = 59). Focal cortical dysplasia account for almost 20 % (n = 55) of the overall developmental anomalies category. Conversely the leading cause of the epilepsies attributed to be genetic in aetiology is tuberous sclerosis (n = 32). Other notable causes of epilepsy in the genetic category include Sturge Weber syndrome (n = 9); neurofibromatosis (n = 8); Angelman syndrome (n = 5); Rett syndrome (n = 5) and SCN1A gene mutation (n = 4). The cause of epilepsy was unknown in 45.6 % (n = 1469) of our patients (Fig. 1).

### 4. Discussion

This current analysis of the aetiologies of the epilepsies in a large tertiary referral centre is notable for several reasons. Firstly, we believe that this is the largest single centre examination of aetiology, with over 3200 patients included. Secondly, this is also the first robust large analysis of aetiology following the publication of updated ILAE 2017 classification system (with its emphasis on the importance of determining aetiology in individual patients). Thirdly, this detailed study

![Table 1](image)

| Acquired Causes | N  | % (Total N = 1321) |
|-----------------|----|-------------------|
| MESIAL TEMPORAL SCLEROSIS | 380 | 28.70 |
| TUMOUR          | 279 | 21.12 |
| TRAUMA          | 248 | 18.77 |
| STROKE          | 151 | 11.43 |
| PERINATAL       | 138 | 10.45 |
| INFECTION TOTAL | 61  | 4.62  |
| ENCEPHALITIS    | 25  | 1.90  |
| MENINGITIS      | 15  | 1.14  |
| INFECTION [NOT SPECIFIED] | 12 | 0.91 |
| ARSCESS         | 6   | 0.46  |
| SSPE            | 1   | 0.08  |
| RUBELLA         | 1   | 0.08  |
| NEUROCYSTERCERCOSIS | 1  | 0.08  |
| METABOLIC       | 29  | 2.20  |
| VASCULAR        | 12  | 0.91  |
| HYDROCEPHALUS   | 6   | 0.46  |
| DEMYELINATION   | 5   | 0.38  |
| SURDURAL HEMORRHAGE | 4 | 0.30 |
| AMYLOID         | 2   | 0.15  |
| CEREBRAL TUBERCULOMA | 1 | 0.08 |
| DEMENTIA/TRAUMA | 1   | 0.08  |
| MS, DEMENTIA    | 1   | 0.08  |
| REYES SYNDROME  | 1   | 0.08  |
| POST DRS        | 1   | 0.08  |
| VASCULITIS      | 1   | 0.08  |

![Table 2](image)

| TUMOUR-related epilepsies by tumor type. | TUMOUR | N | % (TOTAL N = 279) |
|----------------------------------------|--------|---|-------------------|
| ASTROCYTOMA                            | 79     | 27.08 |
| OLIGODENDROGLIOMA                      | 60     | 21.66 |
| MENINGIOMA                             | 37     | 13.36 |
| DNET                                   | 28     | 10.11 |
| TUMOUR [NOT SPECIFIED]                | 28     | 10.11 |
| GLIOMA                                 | 9      | 3.25  |
| GANGLIOGLIOMA                          | 7      | 2.53  |
| GLIOBLASTOMA MULTIFORME                | 7      | 2.53  |
| CRANIOPHARYNGIOMA                      | 3      | 1.08  |
| EPENDYMOMA                             | 2      | 0.72  |
| HEMANGIOPERICYCTOMA                    | 2      | 0.72  |
| HYPOPHALAMIC HAMARTOMA                 | 2      | 0.72  |
| LYMPHOMA                               | 2      | 0.72  |
| METASTASES                             | 2      | 0.72  |
| CHOROID PLEXUS PAPPILOMA               | 1      | 0.36  |
| CARCINOMA                              | 1      | 0.36  |
| CHONDROSARCOMA                         | 1      | 0.36  |
| GANGLIONEURALONAL                      | 1      | 0.36  |
| GLIONEURALONAL                         | 1      | 0.36  |
| MEDULLOBLASTOMA                        | 1      | 0.36  |
| PINEALBLASTOMA                         | 1      | 0.36  |
| PITUATRY CARCINOMA                     | 1      | 0.36  |
| PITUATARY MACROADENOMA                 | 1      | 0.36  |
| SCHWANNOMA                             | 1      | 0.36  |
| PITUATARY ADENOMA                      | 1      | 0.36  |
was possible by examining data contained in an electronic health record (EHR) system, demonstrating the power of EHRs to facilitate ongoing research and audit in epilepsy and other chronic diseases. This opportunity will likely increase also following the use of more widespread EHR systems in the management of patients with chronic disease in the current and post Covid-19 era.

The epilepsies exhibit marked clinical and genetic heterogeneity and the aetiologies underlying them are diverse, complex, and still often poorly understood [1]. Aetiology may inform therapeutic rationale and can be a major determinant of prognosis. There is a relative paucity of large studies in the literature examining the aetiology of the epilepsies within populations (Supporting Table 5: Summary of studies examining epilepsy aetiology). The estimated representation of unexplained aetiologies in adult practise is thought to account for 40 % of epilepsies [11,12] and can be up to 50 % [13]. Our study shows that over 40 % of our patients have acquired symptomatic epilepsies, with the top three aetiologies being hippocampal sclerosis, brain tumor-related epilepsy, and epilepsy secondary to prior traumatic brain injury. Over 13 % of our patient group had epilepsy related to a symptomatic predominantly genetic or developmental cause. The aetiology of the underlying epilepsy was indeterminate or unknown in nearly 46 % of patients attending our department. The ILAE’s 2017 position paper acknowledges the clinical challenges in assigning causality in epilepsy. The 2017 classification suggests that the underlying causes of the epilepsies can be attributed to structural, genetic, metabolic, infectious, or autoimmune aetiologies [6]. In parallel with this, classification systems in epilepsy are dynamic and should reflect advances in knowledge within the field [14].

This recent ILAE proposed classification of the epilepsies also illustrates the advances in epilepsy genomics [6]. Thus, many previously described symptomatic generalised epilepsies can now often be identified based on whether a known pathogenic genetic mutation is identified in a candidate gene, e.g. “STXBP1 encephalopathy” or “KCNQ2 encephalopathy.” However, this is not the case for a significant proportion of patients with epilepsy for whom the exact pathogenesis of their epilepsy aetiology remains undetermined. The ILAE’s 2017 position paper accedes that assigning aetiology to ‘genetic generalised epilepsies’ is at the discretion of the clinician. The heterogenous and complex aetiological basis underlying the idiopathic epilepsies will undoubtedly challenge clinicians when assigning nomenclature and causality descriptors to this patient cohort. It remains to be seen the effects that modern genomic research may incur when assigning aetiology to this patient cohort fifty years from now.

The EPR facilitates analysis of risk factors, semiology, imaging and electroclinical data. The EPR interface enables clinicians to keep track of diagnostic data pertaining to patients and encourages clinicians to reflect on aetiology. Interpreting the significance of risk factors to epileptogenesis when considering aetiology is challenging. Neuroimaging often assists clinicians in determining whether a focal cause contributes to epilepsy and can sometimes elucidate discrete circuits and pathways that contribute to seizure genesis, this can be especially helpful in patients with dual or multiple aetiological causes [15]. There are often a multiplicity of factors underlying aetiology. For example, the pathogenesis of epilepsy in patients with tuberous sclerosis often exhibits an interplay between both structural and genetic factors, each presenting potential different but complementary therapeutic targets [6]. Moreover in other structural epilepsies, direct genetic causes have also been implicated, e.g., mutations in the LIS1 gene on chromosome 17 p13.3 can cause an autosomal recessive form of lissencephaly, while mutations in the doublecortin gene (DCX or XLIS) is X-linked [7,16]. Enhanced MRI and functional radiological techniques have solved many previously “non-lesional” epilepsies in recent years however there is no standardised epilepsy imaging protocol and not all centres have access to SPECT, PET or other advanced imaging acquisition software [17].

Large epidemiological studies conducted to date analysing the aetiologies of the epilepsies across the globe are few. The older Rochester Epidemiology Project and Mayo Clinic study demonstrated how population-based medical records-linkage systems in Minnesota could examine exposures such as head trauma, cerebral infections, tumours, neurodegenerative conditions and perinatal insults to epilepsy [17,18]. Age specific etiological analysis revealed strong associations with infections, tumors, perinatal injury, and trauma in young adults while in adult population, trauma and neoplasms were more common. Cerebrovascular disease represented the most commonly presumed predisposing factor overall, with an incidence of 11 % in the whole population of epilepsy patients [18].

One systematic review examining global epilepsy incidence and prevalence analysing 222 studies found that epilepsies of unknown aetiology and generalized epilepsy were most prevalent. In this study, unknown aetiologies represented a point prevalence of 3 per 1000 [18]. Kariuki et al. examined the sociodemographic and phenotypic characteristics of 2170 patients with a confirmed diagnoses of epilepsy from Tanzania, Uganda, Kenya, Ghana and South Africa [18]. In this study more than half of the cohort examined were children. Perinatal causes, head trauma and encephalopathies respectively accounted for the most common causes of the epilepsies across the sub-Saharan continent. Similar studies from poor economic developing countries demonstrate comparable results. Uttam et al. identified infection (18.2 %) and perinatal insults (13 %) as major causative factors within their cohort of 500 patients in New Delhi, India [19].

As it supports a range of clinical encounters in tertiary neurology centres in Ireland, the volume of individual patient as well as population data in the national epilepsy EPR grows continuously. Utilising the EPR as the platform for launching this study enables our institution to compare our results with previous large-scale studies conducted worldwide. The Irish epilepsy EPR condenses large volumes of data pertaining to semiology and seizure frequency, family history, epilepsy risk factors, current and previous anti-epileptic drug use, and electroencephalography, neuroimaging and genetic tests results. The Epilepsy Aetiology interface prompts clinicians to reflect on the question of aetiology in each doctor-patient clinical encounter (Fig. 2).

Our study has a few limitations. Firstly, there is an inherent selection bias as our institution is the national referral centre for epilepsy surgery in Ireland. The representation of mesial temporal sclerosis and tumors likely reflect referral bias. Replication of this study utilising our methodology in a regional neurology centre would likely yield somewhat different percentage breakdowns for the aetiologies of the epilepsies. Studies analysing patients attending regional hospitals within general neurology departments and between comparable epilepsy centres worldwide would provide more informative epidemiological comparisons. Secondly, as is the case with paper-based records, the data populated within an electronic patient record is user dependent. However, we believe that the quality of our data is in keeping with best international quality standards. Much of the clinical data in our EPR is entered by experienced advanced nurse practitioners in epilepsy and is also entered by neurology residents and epileptologists. Furthermore, the EPR interface subserves an essential educational resource for junior clinicians working in epilepsy clinics.

Of critical importance when reviewing and extracting data from either paper-based or electronic medical records in clinical research are the issues surrounding data and information governance and security. While EPRs can facilitate efficient interrogation of large volumes of data, research utilising EPRs must be conducted judiciously and adhere strictly to ethical regulations. As evidenced by the current challenges faced by the COVID-19 pandemic, the sharing of epidemiological data offers clinicians essential perspectives and experiences pertaining to patient care. Our study presents an insight into the utility of electronic record systems in the care of patients with epilepsy and potential for large scale analysis of clinical data in epilepsy research.

The ‘river of epilepsy’ [20] is becoming deeper and more complex in the genomic era, and increasing information regarding novel causative
genes in epilepsy, greater collaborative partnerships between geneticists, epileptologists and researchers, as well as improved patient advocacy awareness will inevitably reshape what future classification proposals of the aetiologies of the epilepsies will look like.

5. Conclusions

To our knowledge, this is the largest study of the aetiologies in the epilepsies at a single tertiary referral centre and underscores the importance of considering aetiology in light of the 2017 ILAE publication on the classifications of the epilepsies. Our findings suggest that acquired symptomatic epilepsies represent the largest proportion of our institution’s cohort. Hippocampal sclerosis is the most common cause, followed by cerebral tumor, cortical developmental malformations, and post-traumatic epilepsy. Despite advances in imaging and genetics, the aetiology of a patient’s epilepsy is still unclear in 46 % of our patient cohort, illustrating the importance of ongoing work by the epilepsy research community in understanding the full spectrum of aetiology for all our patients. This study also highlights the value of EPR systems in clinical research and audit in epilepsy, facilitating research in large numbers of patients beyond the pre-digital traditional chart review.

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Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2020.08.005.

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