EPILEPSY

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Dear Doctor,

Greetings from Micro Labs. We are happy to bring you "EPILEPSY Newsletter'' which contains latest and interesting news in the field of Neuropsychiatry.

This issue contains:

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An algorithm's diagnostic value for autoimmune epilepsy

About 1% of the world's population suffers from epilepsy, which is one of the more common neurologic disorders. In about one-third of these people, the cause of their seizure problem is still unclear. In spite of the frequent seizures and tendency to go into status epilepticus (SE) during the acute stage of autoimmune encephalitis (AE), the majority of individuals with AE do not eventually become permanently predisposed to seizures.[1] According to reports, immunotherapy is effective in treating antineuronal antibody-positive cases of refractory epilepsy, and early intervention enhances the prognosis for the patient. In this study, a diagnostic method for autoimmune epilepsy will be proposed, and its clinical applicability will be examined.[2]

Board-certified neurologists and epileptologists who suspected an autoimmune aetiology in 60 patients with focal epilepsy participated in the study. The study used the patients' sera or cerebrospinal fluid (CSF) samples to screen for antineuronal antibodies using rat brain immunohistochemistry in order to determine the participation of the autoimmune aetiology. Positive samples had their antineuronal antibodies examined. The algorithm used to analyse the data for all patients was divided into two steps: evaluating clinical characteristics that might indicate autoimmune epilepsy and evaluating laboratory and imaging findings (abnormal CSF findings, hypermetabolism on fluorodeoxyglucose-positron emission tomography, abnormalities on magnetic resonance imaging, and bilateral epileptiform discharges on electroencephalography). In the initial phase, patients were screened and divided into five groups based on the number of aberrant laboratory findings. A receiver-operating characteristic curve analysis was used to determine the algorithm's important cutoff point.

Rat brain immunohistochemistry revealed that 14 of the 60 patients (or 23.3%) were seropositive for antineuronal antibodies. Ten patients had autoimmune encephalitis/epilepsy-related antibodies. Two abnormal findings were determined to be the optimal cutoff point by the cutoff analysis of the number of abnormal laboratory and imaging findings. This resulted in a sensitivity of 78.6%, specificity of 76.1%, and an area under the curve of 0.81.

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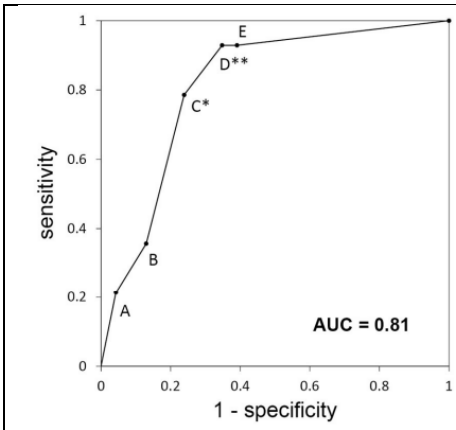

Figure 1: Receiver-operating characteristic curve for the categories of the diagnostic algorithm used for the retrospective cohort.

In this study, a diagnostic method for autoimmune epilepsy without antibody testing was presented. The method's clinical usefulness was then confirmed by retroactively applying it to a cohort that had undergone a thorough antineuronal antibody work-up.[2] This algorithm concentrated on the autoimmune epilepsy characteristics; it did not assess psychiatric symptoms or memory loss, which may result from inflammation, particularly of the medial temporal structures. According to several research, clinical signs of encephalitis are more closely related to antibody positivity than lab results are. According to another study, encephalitis symptoms are linked to strong immunotherapy response.[3]

The suggested approach may be able to identify the underlying autoimmune cause of epilepsy before the findings of antineuronal antibody testing are available.

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Novel Implantable Device for Focal Cortex Stimulation and Antiseizure Results in Two Prospective Multicenter Single-Arm Trials

The fourth most common non-communicable disease affecting years lived with disability worldwide, epilepsy is a dangerous neurological condition that is characterised as experiencing at least two unprovoked seizures in a 24-hour period.[1] Epilepsy affects more than 52 million individuals globally. Refractory status epilepticus (SE) in people without a history of epilepsy and without the discovery of an underlying cause within 72 hours is known as newonset refractory status epilepticus (NORSE).[2] There is a substantial community of persons with drug-resistant epilepsy who require alternative treatment modalities. For the first time, clinical trial results of a novel stimulation tool that has just been available in Europe for the treatment of patients with a predominance seizure focus are described. This study's objectives were to evaluate the feasibility of using the EASEE system for neurostimulation to treat medically resistant focal epilepsy (EASEE II) and to conduct a pilot study to evaluate the feasibility of using patient-controlled neurostimulation to treat medically resistant focal epilepsy using the EASEE system (PIMIDES I).[3]

This study combined the results of EASEE II and PIMIDES I, two nonrandomized uncontrolled trials. The first in-human, prospective, single-arm trials with an 8-month evaluation duration were EASEE II and PIMIDES I. Seven epilepsy centres across Europe recruited patients. Consecutive patients with focal epilepsy who were drug-refractory were enrolled. Patients received the neurostimulation device implant after a one-month prospective baseline period. Unblinded FCS was activated using high-frequency and direct current (DC)-like components through electrode arrays inserted epicranially above the specific epileptic focus region during

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a one-month postimplantation recovery period. Safety and other end goals were evaluated during device implantation and throughout the stimulation period. Efficacy was prospectively evaluated by comparing the responder rate at the sixth month of stimulation to baseline.

The neurostimulation device was implanted in 33 of the 34 adult patients who were enrolled at 6 German and 1 Belgian experimental location (mean [SD] age, 34.6 [13.5] years; 18 male patients [54.5%]). At least until the follow-up appointment at 8 months after the implant, 32 patients underwent combination high-frequency direct current-like stimulation. After six months of stimulation, 17 out of 32 patients (53.1%) were responders to treatment, with at least a 50% decrease in seizure frequency compared to baseline.(Figure 1) This translates to a substantial median seizure reduction of 52% (95% CI, 0.37%-0.76%; P< .001). There were no major adverse events connected to the device or the surgery recorded (0; 95% CI, 0%-10.58%). Cognitive function, mood, or general quality of life did not change significantly.

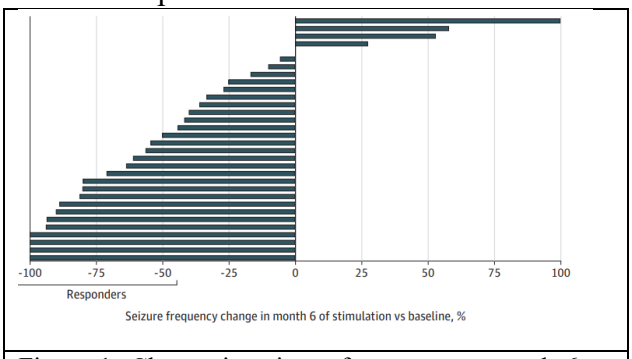

Figure 1: Change in seizure frequency at month 6 vs baseline

Both modelling and experimental recordings demonstrate that subcutaneous electrode implantation enables the exertion of higher effects on neuronal population dynamics in comparison to transcutaneous electrical stimulation.[4] Therefore, it was hypothesised that the treatment intensities used in the trials described here would have an impact on neuronal firing rates, at the very least on the primary neurons in gyral crowns. Combining HFS and DLS, which each have been demonstrated to have antiseizure effects in modelling and experimental approaches as well as under clinical circumstances, was done during stimulation.5 Due to the lack of a control group, there are limitations to the provided data; as a result, it is impossible to exclude the possibility that placebo effects or the influence of measured or unmeasured confounding variables played a role in the observed decrease in seizure frequency.[3]

The findings of this pooled analysis of two nonrandomized, uncontrolled trials indicate that FCS with a novel neurostimulation device was associated with a significant decrease in seizure frequency in patients with drug-resistant focal epilepsy and may represent a promising therapeutic option for patients with a predominate epileptic focus.

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The use of trio-based whole-exome sequencing in the treatment of idiopathic generalised epilepsy

The majority of epilepsy syndromes are those that manifest in otherwise healthy people as widespread seizures with a particular pattern of generalised spike wave (SW) activity with a frequency of 3 Hz on the electroencephalogram (EEG). Idiopathic generalised epilepsies (IGEs), formerly known as genetic generalised epilepsies (GGEs), are assumed to have an idiopathic foundation but are not monogenic (caused by a single gene).[1] The purpose of this study was to investigate the genetic causes of IGEs.[2]

In 60 patients with IGEs, trio-based whole-exome sequencing was carried out. The American College of Medical Genetics and Genomics (ACMG) criteria were used to assess the pathogenicity of potential genetic variations, and the concordance between the reported phenotype and the observed phenotype was used to assess the clinical causation.

Seven unrelated cases of IGE were found to have seven potential variations (11.7%, 7/60). A de novo SLC2A1 (c.376C>T/p.Arg126Cys) mutation found in children with absence epilepsy was assessed as pathogenic with clinical concordance, according to ACMG. Six variations were given unclear significance ratings by ACMG but were later determined to be causal after a review of clinical concordance. In juvenile absence epilepsy, these variants included CLCN4 hemizygous variant (c.2044G>A/p.Glu682Lys) and IQSEC2 heterozygous variant (c.4315C>T/p.Pro1439Ser); in juvenile myoclonic epilepsy, these variants included EFHC1 variant (c.1504C>T/p.Arg502Trp) and CACNA1H (c. Among them, GABRB1 was first recognised as a possible novel IGE causal gene.

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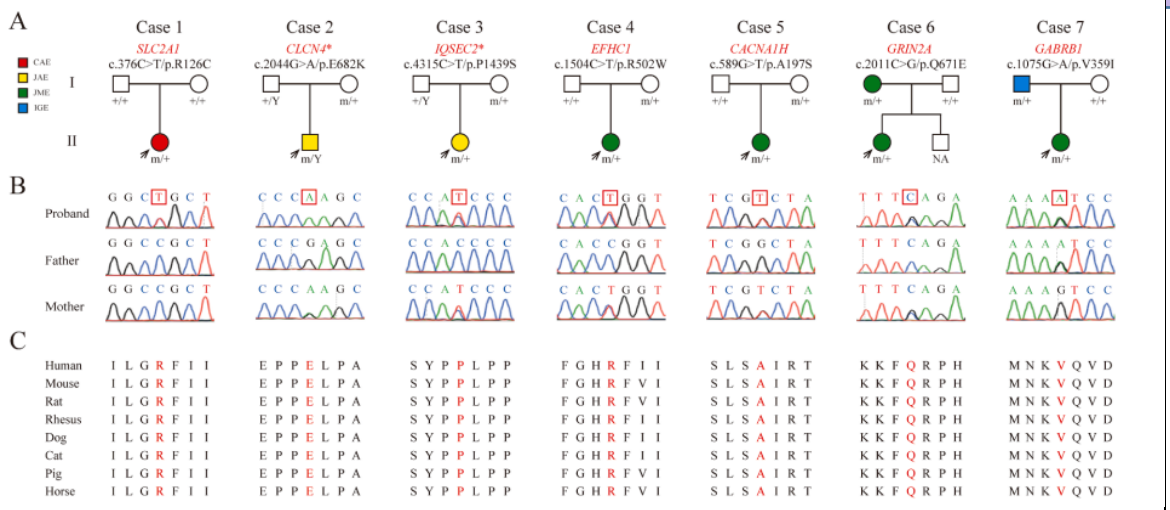

Figure 1: Genetic data of cases with variants

In the current investigation, the researcher found 60 patients with IGEs and identified one putatively causative and six probably causative variations. Reiterating the genetic heterogeneity of IGEs, the seven variations were discovered in seven genes, including three established IGE-associated genes, three genes connected to IGE, and one additional putative IGE-related gene. The value of a thorough study of the pathogenicity of variants based on both ACMG score and clinical concordance assessment is highlighted by the fact that the variants with "uncertain significance" by ACMG were re-evaluated as potentially causative by examining their clinical concordance.Ion channel genes, such as those for the calcium (CACNA1H, CACNG3), GABA (GABRA1, GABRB3, and GABRG2), glutamate (GRM4), acetylcholine (CHRNA4), and chloride channels (CLCN2), are now the ones most frequently linked to 2 CAE.[3]

For the pathogenicity study of variants found in clinical screening, a comprehensive evaluation that combines the ACMG scoring and assessment of clinical concordance is recommended due to the genetic variability and complicated inheritance of IGEs. IGE is likely caused by a novel gene called GABRB1, which calls for more research.

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Epilepsy is a presenting symptom in a case of autosomal recessive intellectual developmental disorder type 5

On the short arm of chromosome 5, the NOP2/Sun RNA Methyltransferase 2 (NSUN2) gene encodes a methyltransferase that is necessary for splicing at the C34 position of the tRNA leu (CAA) and the C47 and C48 positions of the tRNA-asp (GTC).[1] This permits the proper translation of mRNA and the stabilisation of the anticodon-codon pairing.Intellectual disability, facial dysmorphisms, juvenile cataracts, chronic nephritis, hearing loss, seizures, cerebellar atrophy, and microcephaly are only a few of the clinical manifestations caused by NSUN2 gene mutations. While the connection between MRT5 and intellectual disability is well known, there is no data on the link between NSUN2 and epilepsy.[2] In three affected family members of Lebanese descent, Martinez et al. identified an NSUN2 mutation in the homozygous condition, resulting in a Dubowitz-like syndrome marked by mild microcephaly, intellectual impairment, and atypical facies. Only the oldest of the three infected people had epilepsy, and Valproic acid was used to treat seizures.[3] This case study aims to describe the correlation between MRT5 and epilepsy as a phenotypic manifestation, albeit an uncommon one, as the relationship between MRT5 and epilepsy has not been extensively discussed in the present literature.[3]

Case study: This patient was born in Nepal to non-related Nepalese parents at term. The postnatal course of the patient was uneventful. Around a year old, developmental deficits were first observed. His intellectual quotient (IQ) was discovered to be about 40 despite the fact that he has never spoken. He was identified as having both autism and a significant intellectual handicap as a result of these findings. At the age of 8, he underwent a genetic evaluation by a geneticist from a different institution due to concerns about dysmorphic traits, substantial microcephaly, and sensorineural and conductive hearing loss. On examination, folded scrotum and inverted nipples were found. His genetic workup included non-diagnostic karyotype, microarray, fragile X, methylation studies for Angelman syndrome, and biochemical laboratories.

He first experienced a novel form of seizure at the age of 14, one that was accompanied by drooling, eye deviation, and twitching of the mouth. He would slouch over to the left side of his body as well. Each episode would last for 15 to 20 minutes, and tiredness would frequently follow. These incidents happened virtually every day. His 24-hour ambulatory EEG revealed numerous generalised 1-2.5 Hz spike and slow wave discharges, as well as sleep-activated localised epileptiform discharges, without any electrographic seizures (Figure 1).

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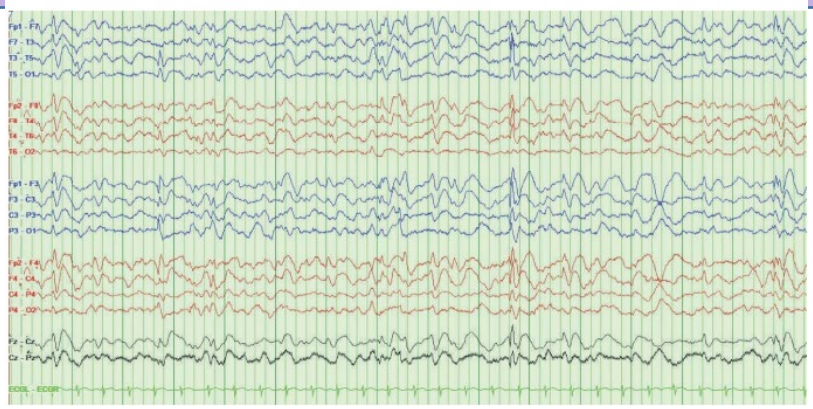

Figure 1: Interictal EEG shows diffuse slowing along with bursts of generalized spike and slow wave discharges.

The work-up was started to determine the cause of the seizures. The results of the brain MRI were unremarkable. A homozygous variant (c.560del; p.Pro187Leufs 8, NM_017755.5) in the NSUN2 gene was identified by genetic testing utilising an Autism/ID Xpanded panel (GeneDx, Bethesda, MD). This variant was confirmed by Sanger sequencing. It is anticipated that NSUN2 will stop functioning as a result of this frameshift version. The patient is nonverbal, cognitively delayed, and disobedient at baseline. His overall tone has risen, and all of his extremities are strong against gravity. Without clonus, deep tendon refexes are consistently 2+. He primarily uses a wheelchair for transportation, but he can walk short distances with help, and his stride is wide-based spastic.

The 15-year-old patient in the case study described in this paper has a history of autism, developmental delay, and focal seizures. The patient possesses a homozygous frameshift pathogenic variation in NSUN2, c.560del; p.Pro187Leufs 8, which is projected to cause a loss of function of the mature protein producing MRT5. This was discovered through an autism/intellectual disability gene panel. The reported literature lists 25 patients with MRT5, the majority of whom have out-of-frame mutations that lead to a loss of function.[1]

The instance in this study emphasises how crucial it is to include genetic testing, such as gene-based panels and whole exome sequencing, in the initial workup for cases with epilepsy with a suspected genetic foundation. Additionally, the seizure drug regimen that this patient took appears to be a workable combination to manage MRT5-related seizures.

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