Understanding Developmental and Epileptic Encephalopathies

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Interview Summary

Developmental and epileptic encephalopathy (DEE) refers to a collection of rare and severe epilepsies that feature both seizures and developmental consequences. In this interview with EMJ, Antonietta Coppola, a consultant neurologist at the University of Naples Federico II, Italy, reviewed the methods for diagnosing DEE, which include a clinical history and physical examination, a prolonged electroencephalogram (EEG), genetic testing, neuroimaging, and testing for possible underlying metabolic disorders. She also discussed the importance of early diagnosis for patients and caregivers. Challenges in management for patients, caregivers, and healthcare professionals (HCP) were highlighted, and Coppola discussed how they might vary according to the patient's age. Coppola concluded with advice for HCPs developing a care plan, and sources of information and support for families.

INTRODUCTION

In 2010, the International League Against Epilepsy (ILAE) defined epileptic encephalopathy as a condition where the epileptic activity itself may contribute to severe cognitive and behavioural impairments, above and beyond what might be expected from the underlying pathology alone.[1] The term DEE was first introduced by the ILAE in 2017, following an accumulation of evidence that the majority of these conditions were due to a genetic mutation, which could lead to developmental consequences independently from the seizure activity and EEG abnormalities.[2,3]

Epilepsy syndromes with onset in childhood are divided into three categories: self-limited focal epilepsies, generalised epilepsies, and DEE.[4] DEE includes a number of conditions, such as Lennox–Gastaut syndrome (LGS), which accounts for approximately 1–2% of all patients with epilepsy.[4] Some 3.6% of all children with epilepsy, and 19.0% of children with seizures starting in infancy, evolve to LGS.[4]

DEEs commonly manifest in infancy and childhood with drug-resistant seizures, epileptiform EEG patterns, developmental slowing or regression, and cognitive impairment.[5] Certain types of seizures are very common in specific DEEs. For example, in LGS, patients may experience tonic seizures, atypical absences, drop (atonic) seizures, myoclonic seizures, and generalised tonic-clonic seizures.[6] Patients may also have neurodevelopmental comorbidities, including autism spectrum disorders, neurological disorders such as cerebral palsy, movement disorders, behavioural disorders, psychosis, and sleep, speech, respiratory, or gastrointestinal disorders.[5]

DIAGNOSIS OF DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES

Coppola discussed the techniques for diagnosing DEEs, and the importance of early diagnosis for patients and caregivers.

How are Developmental and Epileptic Encephalopathies Diagnosed?

The diagnosis of DEEs occurs through a comprehensive approach that includes different, equally important, levels of investigation.[7] First is the clinical history and the physical examination, during which information should be collected about the developmental stages that the child has reached, and whether there have been any delays. Intellectual abilities need to be evaluated through age-appropriate testing. A history of the seizure types and their severity should be recorded, including their duration, and any instances of status epilepticus. Information about drug responsiveness can also assist with diagnosis, including whether a specific drug exacerbates the patient's seizures. Neurological and non-neurological comorbidities should be noted, specifically neurodevelopmental comorbidities. It is important to look for organ involvement, systemic signs, and neurocutaneous syndromes such as tuberous sclerosis complex.

A prolonged EEG should be conducted to examine the epileptiform activity and gain information about intellectual abilities.[8] The EEG can also signpost certain markers of disease. For example, a burst suppression pattern can be suggestive of early infantile DEE.[8] Genetic testing could help identify the precise aetiology.[8] The most widely used technique is next-generation sequencing, using a panel of up to 500 genes known to be associated with DEE. When the results of genetic testing are negative, whole exome sequencing can be considered.

Neuroimaging evaluation should be performed using the gold standard, which is a high-resolution brain MRI.[8] Although most DEEs are due to genetic mutations, metabolic conditions can be causative or contributing factors, and therefore, patients should also receive a metabolic workup.[8] For example, GLUT1 deficiency syndrome is due to a mutation in the *SLC2A1* gene, which codifies GLUT1, the primary transporter of glucose in the brain.[9] Testing glucose levels in the blood and the cerebrospinal fluid can help to diagnose this condition.[9]

Are Developmental and Epileptic Encephalopathies Difficult to Diagnose?

DEEs are challenging to diagnose because of their complexity. The complete clinical picture may be lacking at onset, but over time, new symptoms and test results may raise a suspicion of DEE. For example, seizures may manifest later in the course of the disease, with the genetic aetiology of DEE independently causing developmental impairment in isolation.[10]

Another challenge is that genetic analysis using next-generation sequencing might yield negative results, while whole exome sequencing can report a variant of uncertain significance, or a rare variant in a gene not known to be associated with DEEs.[7] In the latter case, functional studies are needed to reproduce the genetic mutation in cells or animal models, so that the phenotype can be studied, a process which is costly and time-consuming.[7]

What Impact Does Early Diagnosis Have on Patients and Caregivers?

While challenging, the early recognition of a DEE has far-reaching implications for treatment, prognosis, and counselling.[11] DEEs require timely and targeted treatment, and prompt diagnosis enables the best standard of care to be initiated. Potential interventions include surgery, vitamin replacement in cases of pyridoxine (vitamin B6) deficiency, and a ketogenic diet for GLUT1 deficiency syndrome.[8] Early diagnosis also allows appropriate anti-seizure medication (ASM) to be initiated, while drugs associated with seizure exacerbation can be avoided.

Early diagnosis leads to earlier intervention, which can in turn improve prognosis. If making a DEE diagnosis, part of the condition can be remediable with the potential to lead to the reversal of developmental slowing, allowing the patient to make developmental gains and show improvement in cognition.[11,12] The aim of ASM, for example, is to suppress epileptiform activity and reduce seizure severity, thereby aiding developmental and cognitive progress.[12,13] There are, however, specific genetic types of DEEs in which, despite the fact that seizures can be controlled, the developmental outcome will remain poor.[13] This is important information to share with families.

Reproductive counselling is a crucial element of the care process for families asking the question: "Am I going to have another child with the same condition?"[14] The majority of DEEs are due to a *de novo* genetic mutation, meaning the risk is equal to the general population, but some DEEs are caused by a germline mosaicism in one parent, and there is a high risk of recurrence in their offspring.[13,15] It is important to consider the different genetic scenarios through counselling, and to consider the reproductive options available to families.

Although a definitive diagnosis does not always lead to changes in treatment or provide further clarity around prognosis, it is often a relief for families to be able to put a name to their child's condition. In addition, joining dedicated family support groups for specific conditions can provide considerable emotional benefit, by allowing families to find comfort, share information, and source practical solutions for the challenges they face.

What is Your Advice for Achieving Early Diagnosis?

Prompt diagnosis can be achieved by sending patients to a third-level referral centre for immediate investigation. These centres are equipped to undertake the necessary investigations, including genetic analysis, long EEG monitoring, neuroimaging, and metabolic studies.

MANAGEMENT OF DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES

Coppola described the challenges of DEE management for everyone involved and outlined how to devise a care plan.

What are the Challenges in Management for Patients and Carers?

Patients with a DEE need a very high standard of care, which includes frequent investigations and hospitalisations, as well as intermittent intensive care treatment. Precision medicine approaches based on the specific genetic defect can dramatically improve quality of life for patients and families.[7,11,16] However, in some cases, such treatments have not been developed, while in others they exist but are not accessible for all patients, owing to bureaucratic and economic barriers, which can be a difficult reality for families to accept.

Daily management affects the lives of patients, parents, and siblings.[17] The treatment is complex, and requires strict adherence to a fixed schedule, for example, taking an ASM every 3–4 hours to avoid seizures. Medication may also be needed for behaviours and psychiatric symptoms that are challenging to manage. Indeed, behavioural and psychiatric symptoms can be even more challenging for families than seizures themselves, having a profound effect on the family, and social lives of patients and families combined. The care of patients is so intensive, it can often result in situations where more than one adult is required to care for a single child, which can place stress on siblings. Patients with severe DEEs often have feeding difficulties,[17,18,20] breathing issues,[17-19] frequent infections,[20] and as previously mentioned, comorbidities such as movement disorders[17,20] and cerebral palsy.[5] Overall, holistic management of the complex symptoms associated with DEEs is important for the quality of life of the patient and their family.

What are the Challenges in Management for Healthcare Professionals?

Management of patients with a DEE diagnosis is challenging at all stages of the condition. The initial treatment of a DEE must be aggressive, and several ASMs may be used to control seizures, and avoid the developmental consequences of the condition.[11] At the same time, a balance between anti-seizure effect and tolerability should be maintained. This balance is difficult to achieve and must be constantly observed. There are a range of ASMs available, albeit fewer options for children; however, there are no commercially available medications to address intellectual disabilities. This is an area precision medicine can address, but as noted previously, identifying an appropriate precision medicine requires intensive laboratory work and functional studies, and ultimately these therapies may be unavailable or inaccessible.[7]

Do the Management Challenges Vary According to the Patient's Age?

Management of DEE is challenging at all ages, but for different reasons. In the paediatric population, treatment must be aggressive and timely to stop the detrimental effects of seizures and EEG abnormalities, while managing the side effects of ASMs. HCPs should also monitor developmental milestones and intellectual abilities, coordinate rehabilitation and habilitation interventions, and aim to prevent comorbidities.

The priorities of management may change when patients reach late adolescence or adulthood. In some cases of DEE, seizures may settle down (less severe, less frequent, fewer types) or disappear, and the clinical picture is dominated by other symptoms and comorbidities, including behaviours that are challenging to manage, psychiatric symptoms, ataxia, dysarthria, intention tremor, and intellectual disability.[21] Families are often more concerned about the behavioural and psychiatric symptoms, which can deeply affect social and family life, than seizures themselves, which they are more familiar with managing. Adults with DEE do not become autonomous, and their parents may be ageing, and no longer able to care for them, so they may live in communities with shared or less consistent caregivers who may be unfamiliar with the patients' history. Often, there is no transition path from paediatric to adult clinics, and while a child neurologist coordinates care for patients of paediatric age, older patients are often managed by different professionals for each individual problem.

What is Your Advice for Healthcare Professionals Developing a Care Plan?

HCPs developing a care plan should build two networks. First, an inner local network of all professionals involved in diagnosing and managing DEEs, including geneticists, pharmacists, physiotherapists, psychiatrists, neurologists, and neuroradiologists. Second, an outer network in the international community. This is because DEEs are rare and complex conditions, and while HCPs may have several patients with Dravet syndrome or LGS, they might have just one

patient with *STXBP1* encephalopathy. A specialised referral centre for DEEs that is a member of the European Reference Network for Rare and Complex Epilepsies (EpiCARE), for example, will be able to provide advice and support to HCPs.[22]

Where Would You Send Patients and Caregivers for Support and Information?

National and international foundations, such as the Epilepsy Foundation,[23] and the National Epilepsy Support Service,[24] provide support and information for patients with epilepsy, and their families. When a specific diagnosis is made, organisations like the LGS Foundation,[25] and Dravet Syndrome European Federation,[26] offer practical and scientific information about diagnosis and treatment, as well as a supportive community.

CONCLUSIONS

Coppola concluded by reiterating that DEEs are complex conditions, and a concerted effort should be made to reach a precise diagnosis as early as possible. Genetic analysis is urgent and may permit the identification of the most effective treatment. If genetic tests are negative or inconclusive, functional studies are essential for establishing the most appropriate treatment plan. Such studies are time-consuming, expensive, and not available in every centre, but specialised centres may be able to help. HCPs should build their own network of professionals because these complex conditions require a holistic approach, that considers the management of many co-occurring and complex symptoms which cannot be achieved in isolation.

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