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Intellectual Disability and Epilepsy: The High Incidence and the Risks of Status Epilepticus and Sudden Death Require Improved Therapies

Epidemiology of Developmental and Epileptic Encephalopathy and of Intellectual Disability and Epilepsy in Children

Poke G, Stanley J, Scheffer IE, Sadleir LG. *Neurology*. 2023;100(13):e1363-e1375. doi:10.1212/WNL.0000000000206758

Background and Objectives: We aimed to determine the population-based cumulative incidence and prevalence of developmental and epileptic encephalopathies (DEEs) and intellectual disability and epilepsy (ID+E) in children. We analyzed the cumulative incidence of specific epilepsy syndromes. Methods: Children younger than 16 years with a DEE or ID+E were ascertained using EEG records from 2000 to 2016 in the Wellington region of New Zealand. Epilepsy syndromes were diagnosed on medical record and EEG review. Point prevalence and cumulative incidence for children with epilepsy and developmental impairment, DEE and ID+E were calculated. Cumulative incidence for each epilepsy syndrome was calculated. Results: The cohort comprised 235 children (58% male) with developmental impairment and epilepsy, including 152 (65%) with DEE and 83 (35%) with ID+E. The median age of seizure onset was 15.4 months (range day 1-15 years). The median follow-up from seizure onset was 7.9 years (range 0-18.2 years). Point prevalence for the broad group of children with epilepsy and developmental impairment was 175/100,000 children (95% CI 149-203; DEE 112 and ID+E 63/100,000 children). Cumulative incidence for DEE was 169/100,000 children (95% CI 144-199) and that for ID+E was 125/100,000 children (95% CI 95.4-165). Cumulative incidence per 100,000 children was as follows: infantile epileptic spasms syndrome 58.2 (95% CI 45.0-75.3), epilepsy with myoclonic-atonic seizures 16.4 (95% CI 9.69-27.7), Lennox-Gastaut syndrome 13.2 (95% CI 4.1-41.9), and Dravet syndrome 5.1 (95% CI 2.1-12.2). Fifty/152 (33%) of children with DEE and 70/83 (84%) with ID+E could not be diagnosed with a known epilepsy syndrome. Discussion: Epilepsy and developmental impairment before the age of 16 years occurs in 1 in 340 children, with 1 in 590 having a DEE and 1 in 800 having ID+E. These individuals require significant health and community resources; therefore, these data will inform complex health service and education planning. Epidemiologic studies have focused on early childhood-onset DEEs. These do not fully reflect the burden of these disorders because 27% of DEEs and 70% of ID+E begin later, with seizure onset after the age of 3 years. Understanding the cumulative incidence of specific syndromes together with the broad group of DEEs is essential for the planning of therapeutic trials. Given trials focus on specific syndromes, there is a risk that effective therapies will not be developed for one-third of children with DEE.

Rates of Status Epilepticus and Sudden Unexplained Death in Epilepsy in People With Genetic Developmental and Epileptic Encephalopathies

Donnan AM, Schneider AL, Russ-Hall S, Churilov L, Scheffer IE. *Neurology*. 2023;100(16): e1712-e1722. doi:10.1212/WNL.0000000000207080

Background and Objectives: The genetic developmental and epileptic encephalopathies (DEEs) comprise a large group of severe epilepsy syndromes, with a wide phenotypic spectrum. Currently, the rates of convulsive status epilepticus (CSE), nonconvulsive status epilepticus (NCSE), and sudden unexplained death in epilepsy (SUDEP) in these diseases are not well understood. We aimed to describe the proportions of patients with frequently observed genetic DEEs who developed CSE, NCSE, mortality, and SUDEP. Understanding the risks of these serious presentations in each genetic DEE will enable earlier diagnosis and appropriate management. Methods: In this retrospective analysis of patients with a genetic DEE, we estimated the proportions with CSE, NCSE, and SUDEP and the overall and SUDEP-specific mortality rates for each genetic diagnosis. We included patients with a pathogenic variant in the genes SCN1A, SCN2A, SCN8A, SYNGAP1, NEXMIF, CHD2, PCDH19, STXBP1, GRIN2A, KCNT1, and KCNQ2 and with Angelman syndrome (AS). Results: The cohort comprised 510 individuals

with a genetic DEE, in whom we observed CSE in 47% and NCSE in 19%. The highest proportion of CSE occurred in patients with SCN1A-associated DEEs, including 181/203 (89%; 95% CI 84-93) patients with Dravet syndrome and 8/15 (53%; 95% CI 27-79) non-Dravet SCN1A-DEEs. CSE was also notable in patients with pathogenic variants in KCNT1 (6/10; 60%; 95% CI 26-88) and SCN2A (8/15; 53%; 95% CI 27-79). NCSE was common in patients with non-Dravet SCN1A-DEEs (8/15; 53%; 95% CI 27-79) and was notable in patients with CHD2-DEEs (6/14; 43%; 95% CI 18-71) and AS (6/19; 32%; 95% CI 13-57). There were 42/510 (8%) deaths among the cohort, producing a mortality rate of 6.1 per 1,000 person-years (95% CI 4.4-8.3). Cases of SUDEP accounted for 19/42 (48%) deaths. Four genes were associated with SUDEP: SCN1A, SCN2A, SCN8A, and STXBP1. The estimated SUDEP rate was 2.8 per 1,000 person-years (95% CI 1.6-4.3). Discussion: We showed that proportions of patients with CSE, NCSE, and SUDEP differ for commonly encountered genetic DEEs. The estimates for each genetic DEE studied will inform early diagnosis and management of status epilepticus and SUDEP and inform disease-specific counseling for patients and families in this high-risk group of conditions.

Commentary

These 2 new research studies on epilepsies associated with intellectual disabilities (ID) explore several complementary aspects of these conditions, thereby expanding our understanding of these complex disorders. A well-done epidemiologic study in the Wellington region of New Zealand provides a clearer picture of issues surrounding ID and comorbid epilepsy through its use of 2 important methodologic strategies.[1] The first is that the authors distinguished between developmental and epileptic encephalopathy (DEE; in which seizures and epileptiform EEG discharges contribute to the slowing or regression of development) and intellectual disability and epilepsy (ID+E; in which developmental delay is static and may precede seizures).[1] The second is that children were studied up through less than 16 years (rather than up to less than 3 years, as done in prior studies). They examined not only the point prevalence but also the cumulative incidence of these 2 groups. By virtue of a median clinical follow-up period of about 8 years, the authors also studied features including seizure-freedom rates, progression from epileptic spasms (ES) to other syndromes, differing severities of ID in patients with DEE and in children with ID+E, deaths, and the number of resolved epilepsy cases.[1]

The authors found that the cumulative incidence of the combination of DEE and ID+E before age 16 years was quite large: 1 in 340 children.[1] Specifically, the incidence of DEE was 1 in 590 children through childhood and adolescence, which is more than double the incidence found in a Scottish study of DEE with onset before age 3 years.[2] The cumulative incidence of ID+E was 1 in 800 children, and 70% of the latter cases had epilepsy onset between ages 3 and 15 years.[1] This was the first research project to study the latter group and, therefore, to make these findings.

Developmental and epileptic encephalopathy patients were clinically classified by epilepsy syndrome, where possible,[1] according to International League Against Epilepsy (ILAE) definitions.[3] The most common DEE syndrome was ES which had a high cumulative incidence: 1 in 1700 children up to age 2 years. Of those with ES, by age 8 years, 40 (63%) had progressed to other syndromes, 13 had been seizure free for 3 years, and 6 had died. The incidence of epilepsy with myoclonic and atonic seizures (EMAtS; formerly, Doose syndrome) in the present study was 1 in 6094, 3 times higher than that reported in the previous study.[2] The incidence of Lennox-Gastaut syndrome (LGS) was 1 in 7575, which was not higher than in older studies, possibly because the most recent, precise definition of LGS was used.[3] The incidence of Dravet syndrome was 1 in 19 608 children. The incidences of DEE with spike-and-wave activation in sleep (formerly, continuous spike-and-slow waves in sleep),[3] Landau-Kleffner syndrome, and other syndromes were calculated.

Not surprising to clinicians who care for ID patients with epilepsy, the authors determined that one-third of DEE patients (most of whom had a focal DEE) could not be classified into one of the current ILAE-defined syndromes.[1,3] Among the ID+E group, the majority had focal epilepsy also, and 84% could not be diagnosed with an ILAE syndrome. With respect to other features, the overall incidence of epilepsy was highest in the first year of life, the median ages of epilepsy onset were 9.0 and 46.5 months in the DEE and the ID+E children, respectively ($P < .001$), severe to profound ID occurred 3.7 times more often in children with a DEE than with ID+E, mortality was 13% in DEE and 11% in ID+E children, seizure-freedom for 5 years occurred in 27% of DEE and 59% of ID+E children ($P = .01$), and epilepsy resolved in 15.6% of DEE and 48.1% of ID+E children.[1]

In the second article, the rates of convulsive status epilepticus (CSE), nonconvulsive status epilepticus (NCSE), overall mortality, and sudden unexpected death in epilepsy (SUDEP) were investigated in 510 DEE patients in an Australian genetic registry.[4] Although the rates of SE and SUDEP have been well described for Dravet syndrome, these data are less well defined for the more recently identified genetic DEEs. The anticipated risk of CSE, NCSE, total mortality, and SUDEP was calculated for each of 12 genetic DEEs.

The median age was 10 years and 77% were children.[4] Overall, 47% had an episode of CSE and 19% had NCSE. Many patients with *SCN1A* DEEs had CSE: 89% of patients with Dravet syndrome and 53% of patients with other *SCN1A* DEEs. Convulsive status epilepticus was also common in DEE patients with pathogenic variants in *KCNT1* (60%), *SCN2A* (53%), and *STXBP1* (35%) genes. Convulsive status

epilepticus was more common than NCSE in patients with *SCN1A*, *SCN2A*, *SCN8A*, *STXBP1*, *KCNT1*, *KCNQ2*, and *PCDH19* gene variants. Nonconvulsive status epilepticus was more common in non-Dravet *SCN1A*, *SYNGAP1*, *NEXMIF*, and *CHD2* variants, and in Angelman syndrome. The overall mortality rate was 42/510 (8.2%) of patients, equating to 6.1/1000 person-years,[4] higher than found in a Danish study of children with all types of epilepsy.[5] Sudden unexplained death in epilepsy was the cause of death in 48% of patients and occurred only 4 variant genes: *SCN1A*, *SCN2A*, *SCN8A*, and *STXBP1*. The overall SUDEP rate was 2.8/1000 person-years, but the Dravet-specific SUDEP rate was higher at 4.4/1000 person-years. Two genes associated with a high proportion of CSE, *SCN1A* and *SCN2A*, were also associated with SUDEP. A limitation of the second study is that the cohort was based on referral to an epilepsy genetics research program, so no epidemiologic conclusions can be drawn.[4]

These studies elucidate the many clinical, and some societal, issues affecting patients who suffer from epilepsy and ID. The first study indicates how common and severe are DEEs and ID+Es among children. Older research may have underestimated the overall burden of DEEs because of being limited to only selected epilepsy syndromes and to younger age children; 27% of the current study's cases developed epilepsy at ages 3 through 15 years.[1] The children often had ES as their first syndrome, but two-thirds progressed to another clinical syndrome over time, some became seizure-free, and some died. The patients were eventually diagnosed with a variety of DEEs, yet 33% could not be classified into one of the current ILAE-defined syndromes. Interestingly, EMAtS was slightly more common than LGS,[1] yet is under-researched. Developmental and epileptic encephalopathy syndromes had a high rate of severe/profound ID, and both the DEE and ID+E groups had a high mortality rate. There has been a recent trend to research antiseizure medications that will receive regulatory approval for ASMs to reduce seizures in only a few DEE syndromes. These findings indicate a need for future clinical trials to include patients with not only the more popular DEE syndromes (eg, Lennox-Gastaut and Dravet syndromes) but also with EMAtS, rarer DEE syndromes, DEEs of unknown cause, and possibly even patients with ID+E.

The second study[4] identifies the high rate of severe complications like CSE, SUDEP, and general mortality for several gene variants that cause DEEs. This nonepidemiologic study not only also emphasizes the need for new and better therapies, but it also supports the recommendation that genetic testing of epilepsy patients with ID should be performed to potentially guide selection of treatments. The first-ever clinical practice guideline on genetic testing and counseling for unexplained epilepsies was published in 2023 by the National Society of Genetic Counselors[6] and makes recommendations to health care providers who care for people with ID and epilepsy.

David G. Vossler, MD
Department of Neurology
University of Washington System

ORCID iD

David G. Vossler https://orcid.org/0000-0003-4823-0537

Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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