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ENVISIONing a critical period to preserve development: communication delays in SCN1A+ dravet syndrome

Severe Communication Delays are Independent of Seizure Burden and Persist Despite Contemporary Treatments in SCN1A+ Dravet Syndrome: Insights From the ENVISION Natural History Study

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Objective: Dravet syndrome (DS) is a developmental and epileptic encephalopathy characterized by high seizure burden, treatment-resistant epilepsy, and developmental stagnation. Family members rate communication deficits among the most impactful disease manifestations. We evaluated seizure burden and language/communication development in children with DS. Methods: ENVISION was a prospective, observational study evaluating children with DS associated with SCN1A pathogenic variants (SCN1A+ DS) enrolled at age ≤5 years. Seizure burden and antiseizure medications were assessed every 3 months and communication and language every 6 months with the Bayley Scales of Infant and Toddler Development 3rd edition and the parent-reported Vineland Adaptive Behavior Scales 3rd edition. We report data from the first year of observation, including analyses stratified by age at Baseline: 0:6-2:0 years:months (Y:M; youngest), 2:1-3:6 Y:M (middle), and 3:7-5:0 Y:M (oldest). Results: Between December 2020 and March 2023, 58 children with DS enrolled at 16 sites internationally. Median follow-up was 17.5 months (range = 0.0-24.0), with 54 of 58 (93.1%) followed for at least 6 months and 51 of 58 (87.9%) for 12 months. Monthly countable seizure frequency (MCSF) increased with age (median [minimum-maximum] = 1.0 in the youngest [1.0-70.0] and middle [1.0-242.0] age groups and 4.5 [0.0-2647.0] in the oldest age group), and remained high, despite use of currently approved antiseizure medications. Language/communication delays were observed early, and developmental stagnation occurred after age 2 years with both instruments. In predictive modeling, chronologic age was the only significant covariate of seizure frequency (effect size = .52, $P = .024$). MCSF, number of antiseizure medications, age at first seizure, and convulsive status epilepticus were not predictors of language/communication raw scores. Significance: In infants and young children with SCN1A+ DS, language/communication delay and stagnation were independent of seizure burden. Our findings emphasize that the optimal therapeutic window to prevent language/communication delay is before 3 years of age.

Commentary

Dravet syndrome (DS) is a severe, early onset developmental and epileptic encephalopathy (DEE). Typical presentation occurs at age 6 to 12 months with hemi-convulsive febrile status epilepticus (SE). There is subsequent developmental regression and stagnation in the setting of recurrent episodes of SE.[1] Over 80% of cases of DS are due to pathogenic variants in the SCN1A gene causing loss of function in the $Na_v1.1$ subunit within the voltage-gated sodium channel.[2] Children with DS experience progressive communication and motor decline, severe cognitive and behavioral comorbidities, and significantly increased risk of sudden unexpected death in epilepsy (SUDEP)[3] in the setting of increasing seizure frequency.[4] This raises the question whether development and comorbidities can be improved with early optimization of treatment and future disease-modifying therapies.[5–7]

The ENVISION study is a prospective, longitudinal natural history study of developmental outcomes in children with SCN1A+ DS, age 5 years or less at enrollment, with the goal of identifying potential endpoints for future clinical trials.[8] Perry et al. report interim outcomes for children followed at least 1 year looking at seizure burden and communication/language development. Caregiver reported seizure diaries quantified monthly countable seizure frequency (MCSF), rescue medication usage, number of prolonged seizures and SE episodes. Developmental scales included the Bayley Scales of Infant and Toddler Development 3rd edition (BSID-III) for birth to 42 months, the Vineland Adaptive Behavior Scales 3rd edition

(VABS-III) for all ages, and the Weschler Preschool and Primary Scale of Intelligence 4th edition (WPPSI-IV) for ages 2.5 to 7.5 years. The BSID-III was used for some older subjects based on developmental/cognitive status. Communication was evaluated at baseline and Months 3, 6, and 12.

Baseline testing demonstrated significant differences on BSID-III for the youngest and middle age groups (6 months to 2 years and 2 years 1 month to 3 years 6 months, respectively) for mean composite language scores, with the middle age group scoring >2 standard deviations (*SD*) below the expected standard. Strikingly, though the average age of the cohort at baseline testing was 29 months, language skills were on par with neurotypical 13-month-olds. Baseline VABS-III composite scores showed those <2 years were comparable to neurotypical peers, however those ≥2 years had noted communication delays. Longitudinal changes over time demonstrated stagnation and decline in language and communication development. On BSID-III, the overall cohort mean expressive language raw scores increased by 3.1 points/year of chronologic age ($p < .001$) but scaled scores decreased by 1.1 points/year ($p = .012$) indicating slower language acquisition skills. VABS-III mean receptive and expressive raw scores increased 15 points/year before age 2 then slowed to 0.8 points/year. Prior to age 3 years, mean expressive raw scores increased 12.4 points/year then decreased to 4.1 points/year. By age, over a 1-year period, BSID-III in the <2 years group showed language development improved by an age equivalent (AE) of 6 months compared to those in the ≥2 years group who only improved an AE of 1 month. VABS-III showed similar findings in the <2 years group; mean receptive raw scores increased from 27.5 ($SD = 16.4$) at baseline to 38.3 ($SD = 16.1$) at Month 12 (95% CI = 5.7–13.9) while expressive scores increased from 23.7 ($SD = 11.5$) to 35.5 ($SD = 17.0$, mean delta = 11.8, 95% CI = 6.8–16.7). In the oldest age group, expressive communication scores remained essentially unchanged from baseline.

Weak positive correlations were seen between age at first seizure and BSID-III language composite scores ($R^2 = 38\%$) and BSID-III expressive language raw scores and days of rescue medication use ($R^2 = 35\%$). Principal component analysis to evaluate the effect of variant type on language outcomes showed no significant effects.

Limitations include the large amount of parent-reported data including seizure diary entries and responses on VABS-III. Additionally, investigators intended to use scales based on age validated cut-offs, but were limited due to the cognitive level of participants and needed to use BSID-III in older subjects potentially limiting the validity of the assessments.

The ENVISION study demonstrates that stagnation in language development occurs in DS after age 2 years and highlights the importance of natural history studies in rare diseases. Language impairments were seen at baseline in those older than 2 years, but younger participants were closer to neurotypical peers. Despite improvements in identification and optimized therapies for DS,[8] intervention may need to come sooner. Future clinical trials will need to consider a potential cut-off for "developmental rescue" in DS and other epilepsies. This is of immediate significance as antisense-oligonucleotide (ASO) therapies and adeno-associated viral vector (AAV) therapies are being studied.[5,6]

The authors noted a distinct language pattern emerge on VABS-III in 5 children, which could suggest that there are other unique developmental patterns to be identified in DS. It also brings to light a bigger issue: we do not have assessments specific enough for our diseases in pediatric epilepsy. This is clear as the authors needed to use the BSID outside the validated age-range due to the developmental level of the participants. Berg et al. showed that in individuals with DEEs, motor disability raw scores on the Adaptive Behavioral Assessment System-3 could be used to provide a measure of motor ability and mobility when adaptations were made to better fit the population, a technique which could reduce the time and logistical challenges in designing "bespoke" assessments for rare disease trials.[9] The results of the ENVISION trial illustrate clear developmental differences in children with DS compared to neurotypical peers, but are these assessments precise enough for clinical and research purposes? Maybe future trials could include a DS Communication Scale to assess language outcomes more accurately; or maybe a DS Motor Disability Scale would be useful in another scenario.

From other early-onset epilepsies, it's been shown that earlier intervention is key to prevent long-term developmental impairment.[10] We need to intervene early, but how early is early enough? Is there a different intervention set point depending on the genetic syndrome? This study raises important questions and shows us that there is a critical time point for intervention to optimize developmental outcomes in DS.

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