The Effect of Early-Life Seizures on Cognitive and Motor Development: A Case Series

Sandra Jensen-Willett, PT, PhD, PCS; Andrea Cunha, PhD; Michele A. Lobo, PT, PhD; Regina Harbourne, PT, PhD; Stacey C. Dusing, PT, PhD; Sarah W. McCoy, PT, PhD; Natalie A. Koziol, PhD; Lin-Ya Hsu, PhD; Emily C. Marcinowski, PhD; Iryna Babik, PhD; Mihee An, PhD; James A. Bovaird, PhD

Department of Physical Therapy (Dr Willett), Munroe-Meyer Institute, University of Nebraska Medical Center, Omaha, Nebraska; Department of Physical Therapy (Drs Cunha and Lobo), Biomechanics and Movement Science Program, University of Delaware, Newark, Delaware; Department of Physical Therapy (Dr Harbourne), Duquesne University, Pittsburgh, Pennsylvania; Division of Biokinesiology and Physical Therapy (Dr Dusing), University of Southern California, Los Angeles CA; Department of Rehabilitation Medicine (Drs Westcott-McCoy and Hsu), University of Washington, Seattle, Washington; Nebraska Center for Research on Children, Youth, Families and Schools (Drs Koziol and Bovaird), University of Nebraska-Lincoln, Lincoln, Nebraska; College of Human Science and Education (Dr Marcinowski), Louisiana State University, Baton Rouge, Louisiana; Department of Psychological Science (Dr Babik), Boise State University, Boise, Idaho; Department of Physical Therapy (Dr An), Kaya University, Gimhae-si, Gyeongsangnam-do, Republic of Korea.

Purpose: This case series documents developmental changes over time and in response to a novel intervention, Sitting Together and Reaching to Play (START-Play), in children with early-life seizures.
Methods: Thirteen children with early-life seizures were included from a subset of participants in the START-Play multisite, randomized controlled trial. Seven received 3 months of twice weekly START-Play intervention; 6 continued with usual care early intervention. Bayley Scales of Infant Development-III (Cognitive Composite), Gross Motor Function Measure-66 Item Set, Assessment of Problem-Solving in Play, and reaching assessments were administered at baseline, 3, 6, and 12 months postbaseline. Change scores are reported at 3 and 12 months postbaseline.
Results: Over time, plateau or decline was noted in standardized cognition measures; motor development improved or was stable. Children receiving START-Play showed positive trends in problem-solving (71.4%) and reaching behaviors (57.2%).
Conclusions: Interventions such as START-Play that combine motor and cognitive constructs may benefit children with early-life seizures. (Pediatr Phys Ther 2022;34:425–431)
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INTRODUCTION AND PURPOSE

Early-life seizures (ELS), or those diagnosed prior to 3 years of age, are associated with developmental decline.[1-3] In a prospective study of 775 children, Berg et al[1] relate that ELS are indicative of poorer developmental outcomes regardless of underlying causes, comorbidities, or seizure type. In the first year of follow-up postseizure onset, 23% of their sample demonstrated newly recognized developmental delays and 38% of those with mild delays progressed to moderate/severe. These delays were not categorized with respect to specific developmental domains, nor were they quantified with standardized testing.[1]

The cause of developmental plateau or decline related to ELS is multifaceted. Seizures impair neurogenesis and synaptic reorganization, interrupt communication within established neuronal networks, and exacerbate maladaptive plasticity.[2,4] Intellectual disability, decreased psychomotor processing speed, difficulties with fine motor dexterity, and deficits in working memory and visuospatial skills often result.[4,5] Even in the absence of overt seizure activity, underlying electroencephalographic (EEG) abnormalities contribute to atypical neural excitability and disrupt sleep, which is critical for consolidation of learning and memory.[4,6] Given the complexities of ELS and the known effect upon an infant's developing central nervous system, medical management is imperative, yet challenging.

Pharmaceutical interventions prescribed to manage ELS add another layer of developmental complexity. Antiepileptic drugs (AEDs) quiet aberrant neurotransmissions by reducing activity between ion channels, of neurotransmitters, and within second messenger systems in the brain.[7] In the developing brain, neurotransmitters regulate neuronal proliferation, migration,

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Correspondence: Sandra Jensen-Willett, PT, PhD, PCS, Physical Therapy Department, University of Nebraska Medical Center (UNMC), Munroe-Meyer Institute, 985450 Nebraska Medical Center, Omaha NE 68198 (swillett@unmc.edu).

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differentiation, and apoptosis.[8] Altering these processes fundamentally alters central nervous system structure and function. Antiepileptic drugs are associated with central nervous system and developmental sequelae including reduced brain weight and neuronal numbers, underactivation of the brain; psychomotor, behavioral, and spatial learning deficits; impaired learning, attention, and memory; and deficits in verbal fluency and processing.[7,9] Common side effects associated with AEDs, including weakness, dizziness, altered balance, decreased alertness, and increased sleepiness, further complicate how children with ELS engage, learn, and practice developmental skills.[10] Yet, developmental trade-offs between ongoing seizure activity and medical management are poorly understood and withdrawal of or changes in AEDs must occur under medical supervision.[11,12]

Although the adverse effect of seizures and AEDs on standardized indices of development has been reported, understanding how children with ELS respond to focused motor and/or cognitive interventions has not. The purpose of this article is to document developmental changes and explore the effect of a novel intervention, Sitting Together and Reaching to Play (START-Play), in a subset of children with ELS from the larger START-Play multisite randomized controlled trial.[13]

The specific aims were to quantify developmental changes over time and in response to intervention in (1) standardized measures of cognitive and gross motor domains using the Bayley Scales of Infant Development-Third Edition (BSID-III)[14] and the Gross Motor Function Measure-66 Item Set (GMFM-66-IS),[15] respectively; and (2) motor-based problem-solving skills using the Assessment of Problem-Solving in Play (APSP)[16] and a reaching assessment.[13]

START-Play is a unique approach to early intervention that blends motor and cognitive strategies for advancing overall development.[13,17] This approach, in combination with usual care, early intervention services, had positive short-term effects on cognition and problem solving and long-term effects on fine motor and reaching outcomes for children with significant motor delay but with no ELS.[17] Here, we examine the response to START-Play intervention in young children with ELS and motor delays.

SUMMARY OF CASES

A total of 134 children were tested at baseline in the START-Play multisite, randomized, controlled trial (summarized in the studies by Harbourne et al).[13,17] Children enrolled in the START-Play study between the ages of 7 and 16 months corrected age if they were demonstrating (1) motor delays at least 1 SD below the mean on the BSID-III gross motor scale, (2) the ability to prop-sit for at least 3 seconds, and (3) spontaneous arm movements. Uncontrolled seizure activity, per parent report, was an exclusion criterion; however, if parents did not report seizure activity or it was undiagnosed, children were enrolled and randomized.

Thirteen children were excluded from START-Play analysis due to the onset of seizures or poorly controlled seizures during the intervention and/or follow-up period.[17] These are included in this retrospective, case series. All were classified with significant motor impairment, defined as 2.5 SD or greater, below the mean on baseline BSID-III motor composite score. Participant demographics are shown in Table 1.

METHODS/MEASURES

Recruitment and Randomization

For the START-Play trial, children were recruited between 2016 and 2019 from clinical sites in 5 regions of the United States (Seattle, Washington; Richmond, Virginia; Newark, Delaware; Pittsburgh, Pennsylvania; and Omaha, Nebraska). Institutional Review Board approval was obtained from Virginia Commonwealth University and Duquesne University (single Institutional Review Board of record for all sites).

Blocked randomization to usual care or START-Play occurred within the larger cohort (n = 134 randomized) after informed parental consent, eligibility screening, and baseline assessments. Because the initial study was not related to ELS and the research team did not request medical records, no detailed information was obtained on seizure control, frequency or duration, EEG findings, or AEDs for seizure management. Information regarding the child's medical diagnosis, therapy services, and child/family demographics, as well as parental perception regarding effect of each medical issue, including seizures, upon daily life, was ascertained through parental surveys at baseline and upon study completion.

This article reports on a subset (n = 13) of children diagnosed with ELS enrolled initially in the larger study and then excluded from analyses due to the onset of seizures or poorly controlled seizures. Based on the initial START-Play randomization, 7 children with ELS were randomized to the START-Play group and received twice weekly intervention for 3 months (24 visits); 6 were assigned to usual care early intervention. All participants continued with established early intervention, outpatient, recreational, or developmental programs.

Trained physical therapists provided START-Play intervention. They were required to meet and maintain fidelity criteria for key intervention ingredients established by the research team.[17,18] Grounded in the construct of embodied cognition, START-Play emphasizes (1) cognitive and motor activities to create a "just-right challenge" for developmental progress, (2) parent/therapist brainstorming to scaffold cognitive-motor interaction, and (3) motor problem solving and flexibility in movement strategies rather than adherence to "normal movement patterns."[13,17] Analysis of program fidelity demonstrated that therapists trained in the START-Play intervention used the aforementioned therapeutic constructs significantly more than therapists performing usual care.[18] START-Play intervention and fidelity is detailed comprehensively in other publications.[13,17,18]

Assessment Procedures

For the larger study and therefore children in this case series, developmental assessments were performed at baseline and then 1.5, 3, 6, and 12 months after baseline and included measures of sitting, reaching, gross motor skills, problem solving, and parent-child interaction consistent with the model

of change proposed for START-Play intervention.[13] Per caregiver choice, assessments occurred at home, daycare, or research sites. Trained assessors, blinded to subjects' intervention group, completed and videotaped the test battery. The videos were subsequently scored by researchers, also blinded to group assignment. For more information regarding assessment protocols and related reliability, see the study by Harbourne et al.[17] Two of the standardized assessments used, the Bayley Scales of Infant Development-III (BSID-III) and the Gross Motor Function Measure-66-Item Set (GMFM-66-IS), are well-established, psychometrically sound criterion and/or norm-referenced measures designed to track developmental change over time or with intervention.[14,15] Changes in the BSID-III cognitive composite and Gross Motor Ability Estimator (GMAE) computer-tabulated scores from GMFM-66-IS postintervention (3 months after baseline) and 9 months later (12 months after baseline) are reported in this article.

In addition to the BSID-III cognitive and GMAE scores, children were assessed on visual-manual problem-solving skills and reaching behaviors using 2 play-based assessments: the APSP and a standardized reaching task. The APSP is an adapted version of the Early Problem-Solving Indicator. It calculates a single problem-solving score from a weighted model based upon the frequency of 5 behaviors: look (weighted score= 1), simple explore (weighted score = 2), complex explore (weighted score = 5), function (weighted score = 8), or solution (weighted score = 16).[16] Higher weighted scores indicate more complex motor-based problem-solving skills. The APSP was video recorded and blinded coders marked the frequency in which the 5, problem-solving behaviors occurred using Datavyu Software.[16] The APSP demonstrates evidence for construct validity and responsiveness in young children with motor delays. In the START-Play primary analyses sample, APSP scores demonstrated strong positive correlations with BSID-III cognitive scores at baseline and over time.[16] Further details about the APSP and its validity can be found in the study by Molinini et al.[16]

For the reaching assessment, children were tested in a seat that provided trunk support. The reaching assessment consists of 5, 20-second periods where the child was encouraged to interact with an interesting toy at 3 different levels (infant's hip, chest, and eye level). Durations of specific reaching behaviors were normalized to the total assessment duration and expressed as a percentage of time for (1) *total contact with toys* (contact with any hand), (2) *unimanual contact* (1 hand contacts toy), (3) *bimanual contact* (both hands contact toy), (4) *open hand* (contact with at least 2 fingers and thumb extended more than 50%), (5) *looking at toys* (child's eyes focus on object), and (6) *ventral contact* (ventral/palmar side of hand contacts toy).[19,20] Reaching assessments were video recorded and coded by blinded experimenters using Datavyu software. Custom software (Filemaker, version 18, Santa Clara, California) determined instances of co-occurring reaching behaviors: (1) *looking during total contact* (contact while looking at the toy) and (2) *bouts of behavior*—number of times per minute that the child switched among behaviors (normalized to frequency of occurrence per minute). To establish intra and interobserver reliability, 20% of the videos were recoded by blinded assessors. Reliability indices used the equation [Agreed/(Agreed + Disagreed)] × 100.[16,19,20] Intrarater agreement was 95.8 ± 5.5%, and interrater agreement was 93.0 ± 6.9%.

Statistical Analyses

Descriptive characteristics of the sample demographics were reported (Table 1). Change scores from baseline to 3 months and

TABLE 1
Select Demographics of Case Series Cohort

	Medical Diagnosis at Outtake[a]	Age[b] at Baseline in Months	Gender	Race	Family Marital Status	Family Income	Average No. PT/OT/ST Visits per Month[c]	Effect of ELS Upon Daily Life[d]
START-Play group								
1	Dravet syndrome	12	M	White	Married	>80K	11	4
2	CDKL5 deficiency disorder	11	F	White	Married	>80K	4	4
3	CMV, cerebral palsy	9	F	Mixed	Married	>80K	4	4
4	Cerebral palsy	8	M	White	Married	>80K	16	5
5	Infantile spasms	9	M	White	Married	>80K	5	3
6	Seizure disorder	10	M	White	Married	>80K	2	2
7	Sturge-Weber syndrome	9	F	Asian	Married	>80K	6	2
Usual care early intervention group								
8	Prader-Willi syndrome	17	M	White	Married	35-45K	3	1
9	Hydrocephalus	8	M	White	Married	60-80K	3	3
10	Cerebral palsy	16	M	White	Married	>80K	3	4
11	Cerebral palsy	10	F	Black	Married	>80K	2	
12	Cerebral palsy	11	F	Black	Divorced	25-35K	2	5
13	Cerebral palsy	8	M	White	Married	25-35K	<1	2

Abbreviations: CMV, cytomegalovirus; ELS, early-life seizures; F, female; M, male; OT, occupational therapy; PT, physical therapy; ST, speech therapy.
[a]Per parent report at outtake and in addition to a diagnosis of early-life seizures.
[b]Chronological age if term; adjusted age if born preterm (before 37 wk of gestation).
[c]Per parent report over the 12-month duration of study (via service questionnaires at 3, 4, and 5 months and communication with START-Play Interventionists).
[d]Per parent report at outtake using a Likert Scale (0 [not indicated as a concern], 1 [not at all], 2 [minimally], 3 [moderately], 4 [very much], and 5 [extremely]).

TABLE 2

Change in Standardized Measures of Motor and Cognitive Scores at 3 and 12 Months Postbaseline

	Baseline BSID CC	Δ in BSID CC (0-3 mo)	Δ in BSID CC (0-12 mo)	Baseline GMFM-66-IS GMAE Score	Δ in GMFM-66-IS GMAE Score (0-3 mo)	Δ in GMFM-66-IS GMAE Score (0-12 mo)
START-Play group						
1	60	+10	0	30.30	+5.6[a]	+27.4[a]
2	55	0	0	25.20	+0.9	+0.9
3	55	0	0	24.2	−2.7	−0.9
4	70	−5	−15	23.3	+5.4[a]	−1.1
5	55	0	0	19.9	+3.4[a]	+4.3[a]
6	55	0	0	27.8	−2.6	−4.5
7	60	+15	0	31.0	+6.6[a]	+16.6[a]
Usual care early intervention group						
8	85	0	−20	35.6	+0.9	+11.2[a]
9	70	+5	−15	23	+10.6[a]	+13.9[a]
10	55	0	0	18.4	+2.7[a]	−1.2
11	60	0	−5	31.0	+6.6[a]	+4.5[a]
12	55	0	0	23.3	+5.4[a]	+7.7[a]
13	55	0	0	23.3	0	+2.8[a]

Abbreviations: BSID, Bayley Scales of Infant and Toddler Development, Third Edition; CC, Cognitive Composite score (range of 0-100); GMAE, Gross Motor Ability Estimator; GMFM-66-IS, Gross Motor Function Measure-66 Item Set.

[a]GMFM clinically important difference = 1.3, ranging from 2.7 to 1.3 based on Gross Motor Function Classification level.

baseline to 12 months for the cognitive composite (BSID-III) and GMAE (GMFM-66-IS) were tabulated (Table 2); change in duration or frequency-weighted scores of play- and motor-based problem-solving metrics are reported to capture trends over time and in response to intervention (Figure). No group means or between-group comparisons were calculated because of the small sample size and inherent baseline differences between groups (Table 1).

RESULTS

Seventy-one percent (5 of 7) of the children in the START-Play group were White, 57% (4 of 7) were male, and 100% came from families with married parents and family incomes of more than 80K. Sixty-seven percent (4 of 6) of the children assigned to usual care were White, 67% (4 of 6) were male, family incomes were distributed across all levels (Table 1), and all but 1 came from families with married parents. At the end of study participation, seizures were rated as having a moderate to extreme effect upon the child's daily life by parents in 8 of 13 participants.

Standardized Measures of Motor and Cognitive Development

Baseline to 3-month and baseline to 12-month change scores in GMFM-66-IS/GMAE and BSID-III cognitive composite scores by participant are shown in Table 2. Immediately postintervention (baseline to 3 months), 4 of 7 children in the START-Play group demonstrated no change in BSID-III cognitive scores, 1 demonstrated decline in scores, and 2 demonstrated improvement. Nine months after START-Play intervention (baseline to 12 months), 6 of 7 demonstrated no change and 1 demonstrated a decline in cognitive scores. In the usual care group, 5 of 6 children demonstrated no change in BSID cognitive scores at the 3-month assessment and 1 child demonstrated improvement; 3 demonstrated no change at the 12-month assessment; and 3 demonstrated developmental decline. The BSID cognitive composites are norm- and criterion-referenced values that increase over time or in response to intervention.[14] Increasing scores reflect growth in thinking skills.[14]

Four of 7 children in START-Play and 4 of 6 children in usual care exceeded minimally clinically important difference in GMFM-66-IS/GMAE scores at the 3-month assessment (minimally clinically important difference [MCID] = 1.3 points).[21] Nine months after intervention (baseline to 12 months), 3 START-Play children demonstrated a decline and 3 children continued to exceed MCID in GMAE scores. In the usual care group, 5 children demonstrated MCID in GMAE scores at 12 months postbaseline, while 1 showed a decrease.

Play-Based Measures of Motor-Based Problem-Solving and Reaching Behaviors

For problem-solving skills, 5 children (71.4%) participating in START-Play increased the frequency or advanced the complexity of problem-solving behaviors (APSP) from baseline to 3 months and through 12 months; 2 participants in usual care made similar changes over time.

For reaching, 3 children in the START-Play group improved from baseline to 12 months in more than 1 reaching behavior (total contacts, bimanual or unimanual contacts, contacts with open and ventral hand); 1 demonstrated improvement in at least 1 reaching behavior (unimanual contact). Two children in usual care demonstrated improvements over time in at least 1 reaching behavior (bimanual contact); 1 in more than 1 reaching behavior (total contacts, unimanual contacts, contacts with open and ventral hand). Three children in START-Play and 4 in usual care had no changes or developmental decline in reaching behaviors.

A. Change in Assessment of Problem Solving in Play Frequency Weight/Minute at 3 and 12 mo postbaseline (Frequency Weight/Minute is the total score of 5, weighted problem-solving behaviors per minute of play with 3 standard toys)

	APSP Frequency Weight/min Baseline	Δ in Score at 3 mo	Δ in Score at 12 mo
START-Play group			
1[a]	14	**8.83**	**21.83**
2	9.51	−7.84	−6.84
3[a]	0.5	**0.33**	**5**
4	32.67	−16.17	7.5
5[a]	15.67	**2.83**	**16**
6[a]	24	**6.5**	**19.3**
7[a]	38.67	**13**	**39.5**
Usual-care early intervention group			
8[a]	49.67	**16.33**	**45.16**
9[a]	36.33	**13.5**	**24.34**
10	0.67	8.83	4.33
11	68.67	−11.17	1
12	25	−12.67	−9.17
13	7	6.67	2.2

[a]participants who demonstrate pattern of progress across time points.

B. Change in duration of selected reaching variables at 3 and 12 mo postbaseline (duration expressed as percentage of total assessment time)

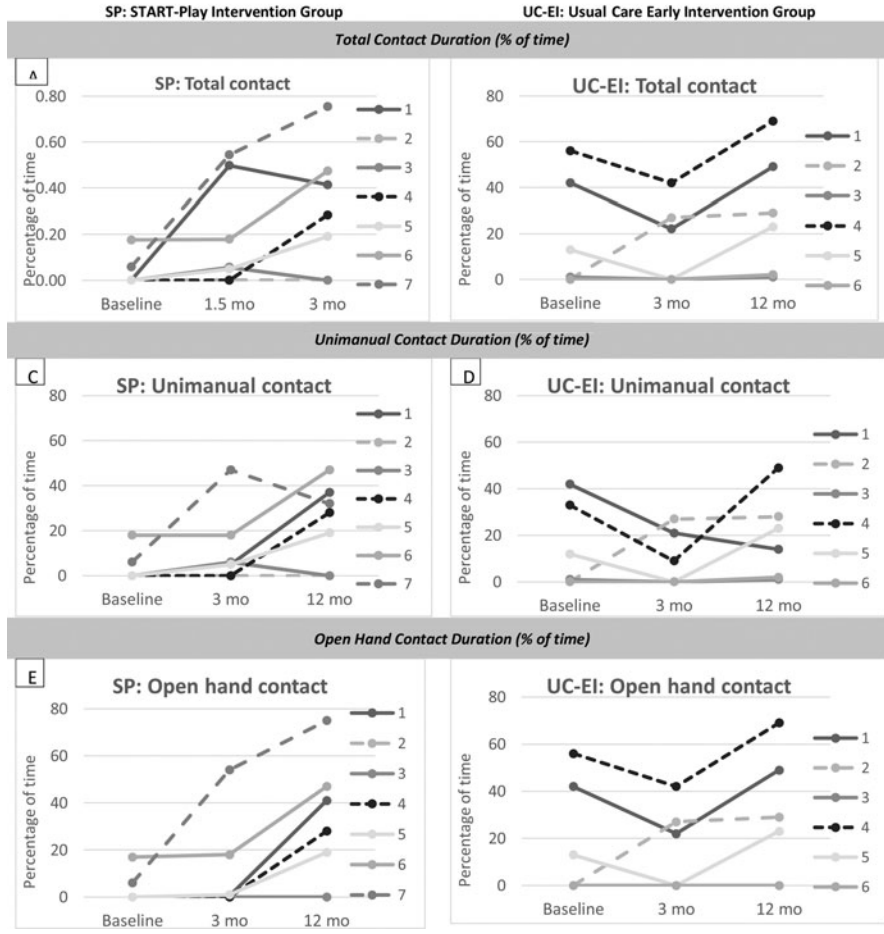

Fig. Summary of individual trajectories in play-based measures of motor-based problem solving and reaching. APSP indicates Assessment of Problem-Solving in Play.

DISCUSSION

Consistent with previous studies, the participants with ELS in this case series had little to no change in response to intervention or over time with standardized measures of cognition (BSID-III). Surprisingly, 2 in the START-Play intervention group were outliers demonstrating a pattern of cognitive progress. Although there is no definitive way to determine how these 2 differed from those who did not make progress with regard to seizure type/frequency or medications or to understand whether progress is related to the START-Play approach, it does invite discussion on whether type and/or frequency of intervention may be important. In all children, "learning," whether in cognitive or motor domains, depends upon high repetition, meaningful practice, and attention to context.[22,23] If ELS

and/or medications that control them disrupt attention, foster neural hyperconnectivity, and destabilize both established neuronal networks and consolidation of learning through sleep, it is feasible that children with ELS require higher frequency of interventions that specifically target motor-based problem solving to impact cognition and drive change.

Lending support to this statement, more children receiving START-Play had improvements in response to intervention and over time in motor-based problem-solving (APSP). It cannot be determined whether this is in response to the intervention approach targeting these behaviors, increased frequency of services, or a reflection of more sensitive, behaviorally based measurement. Tenorio et al[24] discuss the limitations of traditional standardized tests for children with neurodevelopmental disorders stating that floor effects obscure patterns of individual variation and change. These interconnected facts bear consideration: APSP is both a play-and motor-based assessment that considers "real-world" contributions of motor and cognitive constructs within play-based learning, and START-Play intervention intentionally scaffolds this exact type of learning. This may imply that congruency between the selected measurement tools, developmental outcomes, and intervention principles is an important factor when attempting to capture incremental but perhaps important change. In other words, specificity of measurement is just as important as specificity within intervention.

Several authors have related the importance of play-based, observational measures in capturing developmental change in child-directed daily activities and routines, particularly for children with concomitant motor delays.[16,19,20,25] Molinini et al[16] described subtle changes in motor exploration displayed by children with motor challenges that were not captured within the coding structure for the Early Problem-Solving Indicator. "Participants were shifting from modes of simple, high-frequency exploration (mouthing or banging) to more mature goal-directed, low-frequency exploration (trying to fit pieces together or place items in a container)."(p5) This led to refinement of coding to include "simple explore" and "complex explore," capturing an incremental but relevant change in motor-based problem solving, which is now included in the modified APSP. Similarly, Babik et al[19,20] used the standardized reaching assessment in this study to describe incremental but important changes in functional reaching and object exploration during and after intervention with the Playskin Lift exoskeletal garment. They quantified discrete but significant differences in foundational aspects of reaching (unimodal contact, ventral contact, open-hand contact) that was not captured by more global measures of fine or gross motor function.

Measures of motor function (GMFM-66-IS) in this cohort, both over time and in response to intervention, were variable but appeared to demonstrate a pattern of developmental progress. This suggests that ELS and AEDs have less effect upon foundational, ontogenetic motor skills. However, the lack of progress within behavioral reaching measures contradicts this. Reaching is a complex, embodied interaction blending motor, attentional, visuospatial, and perceptual subsystems.[26,27] As such, a behavioral measure of reach captures more than simple biomechanics or motor actions and provides greater sensitivity to change.

Limitations

Without medical records, information regarding seizure type, frequency, and/or medications used for management was not detailed. All are factors known to contribute unique developmental challenges for children with ELS. Understanding why some children demonstrated change compared with others is difficult without medical/diagnostic records. The sample, though randomized within the larger START-Play cohort, was one of convenience that emerged retrospectively. Although this sample is too small to understand measurement bias, the APSP and reaching assessments are recently developed measures of developmental change for which meaningful clinically important differences are not yet established.

Future Research

Prospective, longitudinal studies of children with ELS from onset of seizure activity through early childhood are needed. Studies should consider the multifaceted influence of disease-related variables, "such as the combination of seizure types, seizure frequency, and responsiveness to treatment, disease duration, frequency of epileptiform discharges (on EEG) and specific effects of anti-epileptic medication" (see the study by Ratcliffe et al).[5](p17) Little is understood about how children with ELS change developmentally in motor or cognitive domains over time and in response to any type of early intervention. Selection of responsive, incremental measures of developmental change is crucial. To maximize developmental potential for children with ELS, a better understanding of intervention dose, type, and frequency is necessary.

Clinical Implications

Preliminary evidence suggests that the START-Play approach, which targets motor-based problem-solving skills, jointly advances motor and cognitive abilities in young children with significant motor delays and/or ELS. Assessing motor-based problem solving and the visual-manual changes associated with it over time or in response to intervention requires sensitive, play-based and observational assessment tools. The APSP and reaching assessment used in this study may offer clinicians the opportunity to distinguish incremental changes in motor/cognitive domains. Research is underway to determine whether these tools are feasible to administer and score in clinical contexts.

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