Case Report

Longitudinal neurodevelopmental profile of a pediatric patient with de novo SPTAN1, epilepsy, and left hippocampal sclerosis

C. Luongo-Zink a,b, C. Ammons b, R. Al-Ramadhan i b, R. Logan b, K.E. Ono b,c, S. Bhalla b,c, A. Kheder b,c, D.J. Marcus b, D.L. Drane c,d,e, D.J. Bearden a,c

a William James College, Newton, MA, USA
b Children’s Healthcare of Atlanta, Atlanta, GA, USA
c Department of Neurology, Emory University School of Medicine, Atlanta, GA, USA
d Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA
e Department of Neurology, University of Washington School of Medicine, Seattle, WA, USA

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Pathogenic variants in SPTAN1 result in abnormal neurodevelopment but limited information is available on the spectrum of neurodevelopmental profiles associated with variations in this gene. We present novel data collected at two time points over a three-year period in a nine-year-old patient with heterozygous de novo SPTAN1 variant, drug-resistant epilepsy, and left hippocampal sclerosis. Across evaluations, our patient’s performance was highly variable, ranging from below age expectation to within age-expected range. The patient exhibited relative cognitive strengths at both time points on verbal-expressive tasks. Weaknesses were seen in her attention, executive function, psychomotor processing speed, fine motor, visual-motor integration, and social skills. Memory findings were consistent those associated with left hippocampal sclerosis. Evaluations resulted in diagnoses including attention deficit hyperactivity disorder and autism spectrum disorder.

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1. Introduction

SPTAN1 (spectrin alpha, non-erythrocytic 1) encodes alpha-II spectrin, a component of the spectrin complex, which is involved in various cytoskeletal and developmental processes by forming heterotetramers [1,2]. Pathogenic variants in SPTAN1 have been associated with a spectrum of autosomal dominant developmental and epileptic encephalopathies (DEE), neuropathy, intellectual disability, and autosomal recessive hereditary spastic paraplegia [3–5]. The DEE spectrum is quite broad and includes individuals ranging from profoundly encephalopathic to mildly intellectually disabled patients with and without epilepsy [6]. Genotype-phenotype associations have also been described in relation to this gene, with variants in the last four spectrin repeats affecting the heterodimer formation conferring a dominant negative aggregation effect in individuals with more severe DEE presentations [6] to milder effects on heterodimer assembly in more upstream repeats [7], Fig. 1.

Although patients with pathogenic variants in SPTAN1 often present with cognitive impairment, they may also present with milder or no cognitive deficits. A literature review revealed 12 studies that included patients with likely pathogenic and pathogenic SPTAN1 variants and discussed their intellectual/developmental level [3, 4, 6–15]. Of the 50 patients discussed in those studies, 11 (22%) were classified as profoundly developmentally delayed, 12 (24%) were classified as severely developmentally delayed/intellectually disabled, nine (18%) were classified as mildly to moderately developmentally delayed/intellectually disabled, and 18 (36%) were classified as having normal intelligence or no identifiable cognitive concerns. In addition, a patient in one study was described as having only a severe expressive language impairment [13]. Most patients in these studies did not undergo neuropsychological evaluations. Information on the neuropsychological profile of individuals with SPTAN1 variants is further limited due to the relatively recent discovery of the disorder [15].

In a recent case study that included neuropsychological evaluation, Ylikallio et al. [7] reported on a 20-year-old male with de novo SPTAN1 variant whose neuropsychological evaluation at age 16 demonstrated severe dyslexia, difficulties with executive function, and extremely slow processing speed. His verbal reasoning skills were within age-expected range and his perceptual reasoning...
skills were below average. Additional studies are needed to develop a better understanding of neurodevelopmental profiles in individuals with variants in \textit{SPTAN1} and to monitor their developmental over time.

We present novel longitudinal data on a pediatric patient with de novo heterozygous \textit{SPTAN1} variant, c.2666C > G (p.S889C), a variant not previously described in existing scientific literature. The patient underwent two neuropsychological evaluations approximately three years apart. Her presentation was mild, making it possible for her to undergo comprehensive neuropsychological evaluations. We discuss and compare her performance at the two time points and compare them to findings from the study conducted by Ylikallio et al. [7].

2. Case report

Our patient is a nine-year-old, right-handed female with de novo heterozygous variant in \textit{SPTAN1}. Pregnancy, birth, and perinatal history were uneventful. Early motor development was delayed. Early speech and language skills progressed typically until the patient had her first febrile seizure at 15 months old, after which she became nonverbal. She received early intervention services to treat developmental delays and speech/language skills eventually returned.

The patient’s first febrile (104.7°F) seizure lasted approximately five minutes with decline in oxygen saturation to 40%. She had a second febrile seizure at age four described as upward eye deviation, whole-body shaking, and perioral cyanosis lasting approximately 20 min with a postictal state lasting roughly 40 min. An EEG was within normal age limits and antiseizure medication was not initiated. At age five, the patient began having events described as staring episodes with drooling and unresponsiveness lasting 30–60 s occurring one to two times daily. A routine EEG at that time showed abnormal tracing for age due to focal epileptiform activity was not seen during her episodes of staring and they were deemed to potentially be non-epileptic. The patient also underwent epilepsy gene panel testing that identified a novel heterozygous variant in \textit{SPTAN1} [(NM_001130438.2; c.2666C > G (p.S889C)]. This missense variant falls between spectrin repeats eight and nine of 20. It is absent from healthy population controls (gnomAD) [16]. The patient’s parents tested negative for the \textit{SPTAN1} S889C variant with confirmed parentage and the variant was upgraded in its American College of Medical Genetics [17] classification from variant of uncertain significance to likely pathogenic in classification by the commercial laboratory. Other variants of uncertain significance identified in the patient’s epilepsy panel included \textit{KCNMA1} [(NM_002247.3; c.89A > G (p.H30R)) and \textit{POLG} [(NM_002693.2; c.2632G > T (p.V878L)], which were felt unlikely to be clinically significant due to the inheritance pattern for these genes, their presence in healthy population databases (gnomAD), and overall clinical correlation with our patient’s history.

Following EMU discharge, oxcarbazepine treatment continued due to abnormal EEG findings. She eventually transitioned to lamotrigine due to complaints of gastrointestinal upset associated with oxcarbazepine use. After 17 months without seizures, she was weaned from lamotrigine and subsequently experienced a prolonged seizure with fever that resulted in restarting lamotrigine. Additionally, oral diazepam therapy was prescribed for use at onset of febrile illness for 24 to 48 h to prevent febrile seizures. At six years old, following two years of seizure freedom and a series of normal ECCs she was again weaned from lamotrigine and remained seizure-free. An MRI showed left hippocampal sclerosis (HS) (Fig. 2). Due to ongoing seizure freedom, evaluation for epilepsy surgery associated with HS was not pursued at that time.

Additional medical history included dysautonomia, erythromelalgia, tethered spinal cord, arthromyalgia, osteopenia, hypotonia, vision problems treated with glasses, gastrointestinal and feeding complications, and obstructive sleep apnea treated with CPAP. Medications and supplements at the first neuropsychological evaluation included cannabis for behavior problems and gabapentin for temperature regulation associated with dysautonomia. At the second evaluation, medications included gabapentin, lisdexamfetamine dimesylate for attention deficit hyperactivity disorder (ADHD), vitamin B-2 for stomach pain, and loratadine for allergies.

The patient underwent neuropsychological evaluations at ages seven and nine years old. At both evaluations, parents reported that she had significant self-regulation difficulty that interfered with daily life, including low frustration tolerance, aggression, and impulsivity, and problems following instructions. Kicking, slapping, biting, and pushing were also reported. Additional behaviors included skin picking of her lip, nose, and fingers until she bled. Attention and behavior improved with lisdexamfetamine dimesylate. Social concerns included longstanding difficulty developing and maintaining peer relationships. Restricted interests and repetitive behaviors were noted.

The patient was in first grade during the initial evaluation and fourth grade at the second evaluation. She never repeated a grade. She received special education services beginning in preschool via an Individualized Education Plan (IEP) under Speech/Language Impairment classification. Her first-grade IEP included placement in a general education classroom setting with pullout services for speech/language therapy. Her IEP at the second evaluation included hospital homebound services due to increasing academic and medical problems, one-to-one instruction two hours a day for three days a week, and speech/language and occupational therapies. She received hospital homebound for one year prior to the second evaluation, which improved academic skills.

During her EMU stay, the patient underwent long-term video-EEG monitoring that captured sharp waves originating from the left-greater-than-right occipital region. However, abnormal epileptiform activity was not seen during her episodes of staring and they were deemed to potentially be non-epileptic. The patient also underwent epilepsy gene panel testing that identified a novel heterozygous variant in \textit{SPTAN1} [(NM_001130438.2; c.2666C > G (p.S889C)]. This missense variant falls between spectrin repeats eight and nine of 20. It is absent from healthy population controls (gnomAD) [16]. The patient’s parents tested negative for the \textit{SPTAN1} S889C variant with confirmed parentage and the variant was upgraded in its American College of Medical Genetics [17] classification from variant of uncertain significance to likely pathogenic in classification by the commercial laboratory. Other variants of uncertain significance identified in the patient’s epilepsy panel included \textit{KCNMA1} [(NM_002247.3; c.89A > G (p.H30R)) and \textit{POLG} [(NM_002693.2; c.2632G > T (p.V878L)], which were felt unlikely to be clinically significant due to the inheritance pattern for these genes, their presence in healthy population databases (gnomAD), and overall clinical correlation with our patient’s history.

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**Fig. 1.** MRI brain, T2 sequence, coronal view showing left hippocampal sclerosis (red arrow). For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.
3. Behavioral observations and test results

During both evaluations, rapport was quickly established. The patient wore glasses. Hearing and vision appeared adequate. She was talkative and interactive, but her approach was awkward. Speech was notable for articulation errors and intonation was mechanical and flat. Conversations were brief and centered on her interests. Eye contact was inconsistent; affect was flat. Gestures were awkward or exaggerated. She demonstrated restricted interests, repetitive behaviors, and stereotyped and idiosyncratic language. She understood brief, simple task instructions, but struggled with longer instructions. Self-regulation difficulty was seen at

### Table 1
Neuropsychological tests, scores, and their classifications administered at the first evaluation (age 7 years).

| Intellectual Ability | Standard Score | Percentile | Descriptor |
|----------------------|----------------|------------|------------|
| **Differential Ability Scales-II (DAS-II) Early Years Upper Level** [28] | | | |
| Verbal Cluster | 91 | 27 | Average Score |
| Verbal Comprehension | 88 | 21 | Low Average Score |
| Naming Vocabulary | 96 | 39 | Average Score |
| Nonverbal Reasoning Cluster | 84 | 14 | Low Average Score |
| Picture Similarities | 94 | 34 | Average Score |
| Matrices | 81 | 10 | Low Average Score |
| Spatial Cluster | 75 | 5 | Below Average Score |
| Pattern Construction | 81 | 10 | Low Average Score |
| Copying | 75 | 5 | Below Average Score |
| **Attention/Executive Functioning** | | | |
| BRIEF-2 – Parent Report [29] | T-Score | Percentile | Descriptor |
| Inhibit | 65 | 94 | Potentially Clinically Elevated |
| Working Memory | 75 | 99 | Clinically Elevated |
| Organization of Materials | 67 | 99 | Potentially Clinically Elevated |
| Cognitive Regulation Index (CRI) | 66 | 95 | Potentially Clinically Elevated |
| Global Executive Composite (GEC) | 63 | 93 | Mildly Elevated |
| BRIEF-2 – Teacher Report [29] | T-Score | Percentile | Descriptor |
| Inhibit | 61 | 88 | Mildly Elevated |
| Initiate | 65 | 95 | Potentially Clinically Elevated |
| Working Memory | 73 | 97 | Clinically Elevated |
| Plan/Organize | 61 | 90 | Mildly Elevated |
| Task-Monitor | 61 | 89 | Mildly Elevated |
| Organization of Materials | 72 | 96 | Clinically Elevated |
| Cognitive Regulation Index (CRI) | 68 | 95 | Potentially Clinically Elevated |
| Global Executive Composite (GEC) | 63 | 88 | Mildly Elevated |
| **Visual, Motor, and Sensory** | | | |
| Wide Range Assessment of Visual Motor Ability (WRAVMA) [30] | Standard Score | Percentile | Descriptor |
| Drawing | 72 | 3 | Below Average Score |
| Visual Matching | 47 | 0.02 | Exceptionally Low Score |
| Pegboard – Dominant (Right Hand) | 60 | 0.4 | Exceptionally Low Score |
| Pegboard – Nondominant (Left Hand) | 58 | 0.3 | Exceptionally Low Score |
| **Academic Achievement** | | | |
| Woodcock-Johnson IV (by age) [31] | Standard Score | Percentile | Descriptor |
| Letter-Word Identification | 77 | 6 | Below Average Score |
| Spelling | 59 | 0.3 | Exceptionally Low Score |
| Calculation | 58 | 0.3 | Exceptionally Low Score |
| **Emotional and Behavioral Functioning** | | | |
| BASC-3 Scale Parent [32] | T-score | Percentile | Descriptor |
| Conduct Problems | 63 | 89 | At Risk |
| Somatization | 81 | 99 | Clinically Significant |
| Internalizing Problems | 64 | 91 | At Risk |
| Atypicality | 61 | 86 | At Risk |
| Attention Problems | 61 | 85 | At Risk |
| Functional Communication^ | 32 | 5 | At Risk |
| BASC-3 Scale Teacher [32] | T-score | Percentile | Descriptor |
| Anxiety | 69 | 94 | At Risk |
| Somatization | 111 | 99 | Clinically Significant |
| Internalizing Problems | 85 | 99 | Clinically Significant |
| Attention Problems | 63 | 88 | At Risk |
| Learning Problems | 66 | 91 | At Risk |
| School Problems | 66 | 91 | At Risk |
| Atypicality | 81 | 98 | Clinically Significant |
| Behavioral Symptoms Index | 60 | 86 | At Risk |
| Functional Communication^ | 34 | 8 | At Risk |

Note: Standard score: mean = 100, SD = 15 (lower score = poorer performance). T-Score: mean = 50, SD = 10 (higher score = poorer performance).
Table 2
Neuropsychological tests, scores, and their classifications administered at the second evaluation (age 9 years).

| Intellectual Ability | Standard Score | Percentile | Descriptor                      |
|----------------------|----------------|------------|---------------------------------|
| **Wechsler Intelligence Scales for Children, 5th Edition (WISC-V)** [33] | | | |
| Verbal Comprehension Index (VCI) | 84 | 14 | Low Average Score |
| Similarities | 70 | 2 | Below Average Score |
| Vocabulary | 100 | 50 | Average Score |
| Visual Spatial Index (VSI) | 69 | 2 | Exceptionally Low Score |
| Block Design | 60 | 0.4 | Exceptionally Low Score |
| Visual Puzzles | 85 | 16 | Low Average Score |
| Fluid Reasoning Index (FRI) | 67 | 1 | Exceptionally Low Score |
| Matrix Reasoning | 65 | 1 | Exceptionally Low Score |
| Figure Weights | 75 | 5 | Below Average Score |
| Working Memory Index (WMI) | 74 | 4 | Below Average Score |
| Digit Span | 70 | 2 | Below Average Score |
| Picture Span | 85 | 16 | Low Average Score |
| Processing Speed Index (PSI) | 60 | 0.4 | Exceptionally Low Score |
| Coding | 55 | 0.1 | Exceptionally Low Score |
| Symbol Search | 75 | 5 | Below Average Score |

| Attention/Executive Functioning | Standard Score | Percentile | Descriptor |
|---------------------------------|----------------|------------|------------|
| **WISC-V Digit Span** [33] | | | |
| Digit Span Forward | 75 | 5 | Below Average Score |
| Digit Span Backward | 95 | 37 | Average Score |
| Digit Span Sequencing | 65 | 1 | Exceptionally Low Score |
| **BRIEF-2 – Parent Report** [29] | T-Score | Percentile | Descriptor |
| Inhibit | 75 | 97 | Clinically Elevated |
| Behavioral Regulation Index (BRI) | 71 | 95 | Clinically Elevated |
| Shift | 84 | 99 | Clinically Elevated |
| Emotional Control | 64 | 92 | Mildly Elevated |
| Emotional Regulation Index (ERI) | 74 | 99 | Clinically Elevated |
| Initiate | 70 | 99 | Clinically Elevated |
| Working Memory | 77 | 99 | Clinically Elevated |
| Plan/Organize | 63 | 95 | Mildly Elevated |
| Task-Monitor | 65 | 93 | Potentially Clinically Elevated |
| Organization of Materials | 71 | 98 | Clinically Elevated |
| Cognitive Regulation Index (CRI) | 74 | 98 | Clinically Elevated |
| Global Executive Composite (GEC) | 75 | 99 | Clinically Elevated |

| Visual, Motor, and Sensory | Standard Score | Percentile | Descriptor |
|---------------------------|----------------|------------|------------|
| **Beery VMI-6** [34] | | | |
| Visual-Motor Integration | 67 | 1 | Exceptionally Low Score |
| Visual Discrimination | 83 | 13 | Low Average Score |
| **Lafayette Grooved Pegboard** [35] | Standard Score | Percentile | Descriptor |
| Dominant Hand | 27 | <0.01 | Exceptionally Low Score |
| Non-dominant Hand | 63 | 1 | Exceptionally Low Score |

| Language and Verbal Skills | Standard Score | Percentile | Descriptor |
|---------------------------|----------------|------------|------------|
| **Peabody Picture Vocabulary Test-5 (PPVT-5)** [36] | | | |
| Total Score | 59 | 0.3 | Exceptionally Low Score |
| **Expressive Vocabulary Test – 3 (EVT-3)** [37] | Standard Score | Percentile | Descriptor |
| Total Score | 82 | 12 | Low Average Score |

| Verbal Memory | Standard Score | Percentile | Descriptor |
|----------------|----------------|------------|------------|
| **Children’s Memory Scale (CMS)** [38] | | | |
| Stories Immediate | 70 | 2 | Below Average Score |
| Stories Delayed | 70 | 2 | Below Average Score |
| Stories Delayed Recognition | 80 | 9 | Low Average Score |

| Visual Memory | Standard Score | Percentile | Descriptor |
|----------------|----------------|------------|------------|
| **Children’s Memory Scales (CMS)** [38] | | | |
| Dot Locations – Learning | 65 | 1 | Exceptionally Low Score |
| Dot Locations – Short Delay | 70 | 2 | Below Average Score |
| Dot Locations – Long Delay | 90 | 25 | Average Score |

| Academic Achievement | Standard Score | Percentile | Descriptor |
|----------------------|----------------|------------|------------|
| **Wechsler Individual Achievement Test – IV (WIAT-4)** [39] | | | |
| Subtests | | | |
| Word Reading | 85 | 16 | Low Average Score |
| Reading Comprehension | 67 | 1 | Exceptionally Low Score |
| Math Problem Solving | 68 | 2 | Exceptionally Low Score |
| Pseudoword Decoding | 88 | 21 | Low Average Score |
| Numerical Operations | 76 | 5 | Below Average Score |
| Spelling | 81 | 10 | Low Average Score |
both evaluations but was significantly worse at the initial evaluation and resulted in shortening of the test battery. Improvement between evaluations was consistent with use of lisdexamfetamine dimesylate at the second evaluation. She preferred her right hand and had poor graphomotor control. Gross-motor function included a wide-based gait. Findings were considered valid.

The patient’s neuropsychological performance at both time points was highly variable (Tables 1 and 2), rendering estimations of her overall intellectual ability invalid. Similarities across the two evaluations included relative strengths in verbal expression and weaknesses in attention, executive function, psychomotor processing speed, fine motor, visual motor integration, and social skills. Due to self-regulation problems at the initial evaluation, learning and memory testing was not conducted. At the second evaluation, the patient’s immediate recall of auditory-verbal and visual-spatial information was well below age expectation (Table 2). Following a delay, visual-spatial recall was age appropriate whereas auditory-verbal recall remained weak, improving only marginally when recognition cues were provided. Evaluation findings resulted in diagnoses including ADHD and autism spectrum disorder.

Evaluation recommendations following the initial neuropsychological evaluation included increasing frequency and duration of speech/language therapy, adding occupational and physical therapies to her treatment regimen, and psychiatric consultation to trial stimulant medication, all of which parents reported to have been helpful for the patient. Recommendations from the second evaluation included applied behavioral analysis therapy to manage behavior problems, continued treatment with lisdexamfetamine dimesylate, increased frequency and duration of occupational therapy, and increased academic support across subjects.

4. Discussion

Our case study is one of the first to present neuropsychological data on a pediatric patient with a mild form of SPTAN1 associated cognitive disorders, and the first to present data on the SPTAN1 S889C variant. Multiple lines of computational evidence predict this variant has a deleterious effect on protein structure and function (CADD 25.5 [18], SIFT 0.002 [19], PolyPhen-2 1.00 [20]) and is responsible for a wide range of neurodevelopmental disorders [13 16]. Further, this case is consistent with other cases involving missense variants in the upstream spectrin repeats [6].

A strength of our study is its longitudinal nature that includes neuropsychological data obtained from two time points, findings from which are similar to those from a previous study by Ylikallio et al. [7] that indicated deficiencies in intellectual, executive function, and psychomotor abilities, and relative strengths in verbal expression in a 16-year-old male with a frameshift variant in SPTAN1 evaluated at one time point. A discrepancy between the two studies was seen in word reading ability; our patient exhibited a relative strength in this skill compared to the patient evaluated by Ylikallio et al. [7]. Additionally, our patient has a missense variant that is predicted to result in abnormal protein structure or function with perhaps milder effects on heterodimer formation. In contrast, Yikallio et al.’s patient [7] has a frameshift variant that is predicted to result in a truncated or absent protein product. When compared to severely intellectually disabled patients with SPTAN1 associated disorder [8 15], similarities with our patient include motor impairment and poor attention. Together with Yikallio et al.’s study [7], our work provides a growing understanding of the range of neurodevelopmental profiles associated with variation in SPTAN1 and highlights the importance of neuropsychological evaluations in clarifying individual phenotypes and tailoring interventions.

Another unique aspect of the current study is that our patient only experienced febrile seizures and was seizure-free and off antiseizure medication at age six years old. She also developed left HS, possibly associated with her history of prolonged febrile seizures [21]. Neuropsychological findings were consistent with those associated with left HS. The patient’s delayed spontaneous recall of...
auditory-verbal information was notably weaker (+1 standard deviation) than her delayed recall of visual-spatial information. Even with recognition cues, verbal memory performance remained below age expectation. These findings are consistent with research by Persike et al. [22] that implicated involvement of SPTAN1 variants in mesial temporal lobe epilepsy via downregulation of SPTAN1 protein isoform three in patients with mesial temporal lobe epilepsy when compared to healthy control patients. An additional novel discovery in the current study was that patients with de novo heterozygous SPTAN1 associated disorder may benefit from lisdexamfetamine dimesylate to manage cognitive and behavioral self-regulation problems and improve school performance.

Our patient was also treated with gabapentin at both evaluations to manage symptoms of dysautonomia. Gabapentin affects function of calcium channels [23] and may negatively influence memory, attention, and executive function [24 25]. In addition, cannabisoil was used to manage behavior problems at her initial evaluation, which may stabilize or enhance attention and working memory [26 27].

5. Conclusion

Our case study presents novel longitudinal neuropsychological data on a patient with epilepsy, left HS, and heterozygous de novo SPTAN1 S889C variant. We add to the growing literature regarding the range of neurodevelopmental profiles associated with variants in SPTAN1. At two evaluations across a three-year period, our patient exhibited relative strengths in verbal expression and weaknesses in attention, executive function, psychomotor processing speed, fine motor, visual motor integration, and social skills. Neuropsychological findings were generally consistent with those identified in a study by Ylikallio et al. [7] involving a 16-year-old male with a frameshift variant in SPTAN1. Additional comorbidities included focal epilepsy, left HS, ADHD, and autism spectrum disorder. Attention and behavioral problems and school performance improved following treatment with lisdexamfetamine dimesylate.

Ethical Publication Statement

All authors of this manuscript reviewed this journal’s ethical publication guidelines and affirm that this report is consistent with those guidelines (per the Declaration of Helsinki). The patient and her parents provided informed consent prior to participation in our clinical research.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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