Case Report

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

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ABSTRACT

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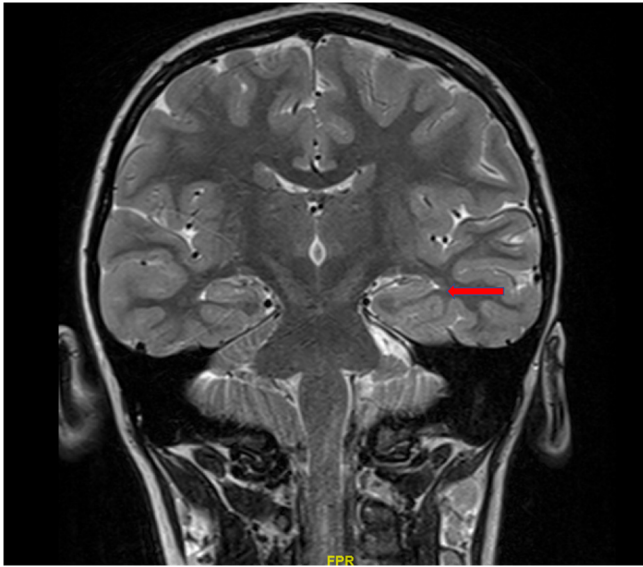
Fig. 1. MRI brain, T2 sequence, coronal view showing left hippocampal sclerosis (red arrow). For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

skills were below average. Additional studies are needed to develop a better understanding of neurodevelopmental profiles in individuals with variants in *SPTAN1* and to monitor their developmental over time.

We present novel longitudinal data on a pediatric patient with de novo heterozygous *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 *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 discharges seen over the left parietal and temporal regions with normal background and sleep architecture; no electrographic seizures were captured. The patient was treated wtih oxcarbazepine and titrated to 20 mg per day but this failed to control her episodes of staring. She was then admitted to our epilepsy monitoring unit (EMU) for further evaluation.

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 *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 *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 *KNCMA1* [(NM_002247.3); c.89A > G (p.H30R)] and *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 EEGs 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 cannabidiol 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.

Table 1

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

Intellectual Ability			
Differential Ability Scales-II (DAS-II) Early Years Upper Level [28]	Standard Score	Percentile	Descriptor
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	66	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
Subtests			
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).

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 2

Neuropsychological tests, scores, and their classifications administered at the second evaluation (age 9 years).

Intellectual Ability			
Wechsler Intelligence Scales for Children, 5th Edition (WISC-V) [33]	Standard Score	Percentile	Descriptor
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			
WISC-V Digit Span [33]	Standard Score	Percentile	Descriptor
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			
Beery VMI-6 [34]	Standard Score	Percentile	Descriptor
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			
Peabody Picture Vocabulary Test-5 (PPVT-5) [36]	Standard Score	Percentile	Descriptor
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			
Children's Memory Scale (CMS) [38]	Standard Score	Percentile	Descriptor
Stories Immediate	70	2	Below Average Score
Stories Delayed	70	2	Below Average Score
Stories Delayed Recognition	80	9	Low Average Score
Visual Memory			
Children's Memory Scales (CMS) [38]	Standard Score	Percentile	Descriptor
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			
Wechsler Individual Achievement Test – IV (WIAT-4) [39]	Standard Score	Percentile	Descriptor
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

Table 2 (*continued*)

Intellectual Ability			
Wechsler Intelligence Scales for Children, 5th Edition (WISC-V) [33]	Standard Score	Percentile	Descriptor
Adaptive Behavioral Functioning			
Adaptive Behavior Assessment System, Third Edition (ABAS-3) – Parent [40]	Standard Score	Percentile	Descriptor
Composite Index Scores			
General Adaptive Composite	71	3	Below Average Score
Conceptual Composite	76	5	Below Average Score
Social Composite	80	9	Low Average Score
Practical Composite	66	1	Exceptionally Low Score
Emotional and Behavioral Functioning			
BASC-3 Scale Parent [32]			
Clinical and Adaptive Scales	T-score	Percentile	Descriptor
Somatization	61	87	At Risk
Withdrawal	62	87	At Risk
Autism and Social Perception Measures			
Social Responsiveness Scale − 2 (SRS-2) [41]	T-score	Percentile	Descriptor
Social Awareness	68	96	
Social Cognition	78	99	
Social Communication	67	96	
Social Motivation	71	98	
Restricted and Repetitive Behaviors	72	99	
Social Communication Index	73	99	
Restricted Interests & Repetitive Behaviors	72	99	
Total Score	74	99	Moderate Range
Autism Diagnostic Observation Schedule, Second Edition (ADOS-2), Module 3 [42]	Comparison Score		Classification/Descriptor
Total Raw Score (in parentheses)	(12)7		Autism/Moderate level of ASD-related symptoms

Note: Standard score: *mean* = 100, *SD* = 15 (lower score = poorer performance). *T-Score*: mean = 50, *SD* = 10 (higher score = poorer performance).

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 neurodevelopment 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 anti-seizure 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, cannabidiol 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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