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Research Article

Impact of Levetiracetam Therapy on Seizure Control and Cognitive Outcomes in Children with Epilepsy

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ABSTRACT

Objective: Levetiracetam (LEV) is effective in seizure control and has a full spectrum of effects on cognitive development, neuropsychological, and behavioral outcomes in children with newly diagnosed epilepsy over 12 months.

Material and Methods: A prospective, multicenter, longitudinal, observational, cohort study was designed. Five tertiary epilepsy centres in Pakistan. Baseline and 6- and 12-month cognitive and behavioral assessments included the Wechsler Intelligence Scale for Children (WISC-V), the Neuropsychological Assessment, and the Child Behavior Checklist (CBCL). In addition, serum LEV trough concentrations and SV2A polymorphisms were evaluated.

Results: 342 patients were enrolled, with 310 patients having completed the 12-month follow-up. By 12 months, 74.2% of patients had ≥50% of their seizures reduced and 58.4% became seizure-free. Cognitive testing demonstrated an average or enhanced full-scale IQ and certain domains of cognition ($p < 0.05$). Behavioral assessments did, however, show statistically significant elevations of externalizing behavior from the CBCL ($p > 0.05$), with higher serum LEV levels and faster titration rates being correlated.

Conclusion: Levetiracetam is well-established as a very effective agent for the control of pediatric epilepsy and has a favorable cognitive-sparing profile. But it has a high risk of behavioral side effects, especially behaviors that are externalized. Routine behavioral monitoring with careful titration iskey to optimizing therapeutic outcomes.

Keywords: Levetiracetam (LEV), Cognitive Outcomes, Seizure Control, Pediatric Epilepsy.

INTRODUCTION

Epilepsy is one of the most common childhood chronic neurological disorders, affecting about 0.5% to 1% of the child population worldwide.[1] Epilepsy in childhood not only poses a direct threat to life from frequent seizures, but it also has a significant effect on neurodevelopment, mental health and quality of life for the child and their family.[2] The risk of cognitive and behavioral comorbidities is an important issue in the treatment of pediatric epilepsy. The problem has been separating and identifying the cognitive deficits arising from underlying epileptic encephalopathy from the cognitive deficits induced using traditional anti-seizure medications (ASMs).[3] This has resulted in a therapeutic paradigm change in pediatric epileptology from absolute seizure freedom to optimizing seizure control and neurocognitive preservation.[4] Recurrent epileptiform discharges, especially during critical periods of brain development, may disrupt synaptic plasticity, affect the connectivity of neural networks, and impair memory consolidation.[5]

In addition, the etiology underlying the epilepsy, including cortical malformations and genetic mutations, is independent to cognitive deficits.[6] In general, the older generation of ASMs are very effective at controlling seizures but can also cause heavy cognitive dulling, psychomotor slowing and impact on attention

and memory.[7] These cognitive impairments can result in ineffective use of medications, academic underperformance, and reduced long-term psychosocial outcomes.[8] Hence, the emergence of newer generation ASMs, claimed to have a more favorable cognitive and side effect profile, have changed the treatment landscape. Levetiracetam (LEV) is a pyrrolidine derivative that is one of the most widely prescribed first-line ASMs for pediatric epilepsy since its approval.[9]

LEV does not directly modulate voltage-gated sodium channels or augment gamma-aminobutyric acid (GABA)ergic inhibition; instead binds specifically to the synaptic vesicle glycoprotein 2A (SV2A).[10] LEV is thought to decrease hyper-synchronization of neuronal networks and to be able to inhibit the presynaptic release of excitatory neurotransmitters while leaving normal low-frequency synaptic transmission unaffected.[11]

In addition, the link between the various LEV serum levels, the SV2A genetic polymorphisms and the development of BAEs is not completely understood.[12] There are limitations inherent in cross-sectional studies such as the problems of selection bias and baseline cognitive differences and practice effects due to repeated testing.[13] Furthermore, the distinction between a real cognitive decline and cognitive testing being interfered by behavioral factors (e.g., a child failing a test because he is irritable) is a methodological challenge that should be addressed.[14]

This study aims to bridge the existing gaps in literature by conducting a rigorous, prospective, multicenter evaluation of the impact of LEV therapy on both seizure control and comprehensive cognitive and behavioral outcomes in children with newly diagnosed epilepsy.

MATERIAL AND METHODS

This study was designed to be a prospective, multicenter, longitudinal observational cohort over a period of 12 months, from January 2024 to December 2024. The study protocol was approved by the Institutional Review Board (IRB) of each participating center (Primary IRB Approval No. PED-NEURO-2021-089) and was carried out following the principles of the Declaration of Helsinki. The inclusion criteria were confirmed diagnosis of epilepsy per ILAE criteria (2014 version), ≥4 seizures unprovoked by a prior seizure within 3 months of the time of enrollment, and baseline normal hepatic and renal function, with provision of written informed consent by parents/legal guardians and written assent by children ≥8 years old. Patients with known hypersensitivity to levetiracetam, severe congenital anomalies, uncorrected sensory deficits (blindness or deafness) or severe intellectual disability (Full-Scale IQ < 50) were excluded to minimize confounding variables, as were patients with a history of severe psychiatric disorders, such as autism spectrum disorder (ASD) or severe attention-deficit/hyperactivity disorder (ADHD) diagnosed before the onset of epilepsy, and patients using medications known to significantly affect cognitive function (e.g. systemic corticosteroids, psychostimulants). All subjects were started with levetiracetam (LEV) oral solution or tablets, as monotherapy, upon enrollment. The first scheme of treatment was uniform between all centres, starting with 10-20 mg/kg/day, split into two equal doses. The dose was increased by 10-20 mg/kg/day every 1-2 weeks depending on clinical response and tolerability, with a target maintenance dose of 30-60 mg/kg/day or a maximum of 3000 mg/day. The timing of clinical follow-up visits was planned at 1 month, 3 months, 6 months and 12 months after treatment initiation. AEs were recorded at each visit on a standardized pediatric adverse event questionnaire and severity was defined based on Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. To measure intelligence and cognitive functioning, the Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V) was used. The main outcome measure was the Full-Scale Intelligence Quotient (FSIQ). Secondary cognitive domains assessed were the Primary Index scores of the Verbal Comprehension (VCI), Visual Spatial (VSI), Fluid Reasoning (FRI), Working Memory (WMI), and Processing Speed (PSI). The Developmental Neuropsychological Assessment, Second Edition (NEPSY-II) was used to assess executive functioning and specific neuropsychological domains. Based on the child's age and baseline functioning, subtests that measure attention and executive functioning, language, and memory were chosen (e.g., Trail Making, Flanker Inhibitory Control, Word Generation, List Memory). The Child Behavior Checklist (CBCL) filled out by the primary caregiver was used to measure behavioral and emotional outcomes. The CBCL provides T scores for internalizing problems, such as anxious/depressed and withdrawn behaviors, externalizing problems, such as

aggressive behavior and rule-breaking, and total problems. T scores ≥ 65 were considered clinically significant. Venous blood samples were drawn at 6-month and 12-month visits – at the same time of day (12 hours post dose) – to estimate steady-state serum LEV trough concentrations for the purpose of investigating pharmacokinetic-pharmacodynamic relationships. HPLC-MS/MS was used to quantify serum levels and a validated method was developed. In addition, a subset of participants (n=150) gave agreement for a pharmacogenetic analysis. Polymorphism in the SV2A gene (rs3766128 and rs10494694) was genotyped by TaqMan allele discrimination assays to examine the possibility of a genetic predictor of cognitive and behavioral outcomes. Sample Size Calculation The sample size was derived for the key cognitive outcome (WISC-V FSIQ baseline to 12-months). Considering a typical standard deviation of 12 points for changes in FSIQ, a two-tailed alpha of 0.05 with a power of 0.8, a minimum of 285 patients was needed. Data was analyzed by R statistical software (Version 4.2.1) and SPSS (Version 28.0). Means ± standard deviations (SD) and medians ± interquartile ranges (IQR) were used to present continuous variables depending on the normality of the data, assessed by Shapiro-Wilk test. The fixed effects were time, age, sex, epilepsy syndrome, and LEV serum concentration. The outcomes of seizures were assessed by Kaplan-Meier survival analysis of time to first seizure and time to 12-month seizure freedom, compared by the log-rank test. Multivariable logistic regression was used to determine the association of LEVs with SV2A genotypes and of the incidence of behavioral adverse events with LEVs, adjusting for age, sex, and baseline CBCL scores. All statistical analyses were performed with a P value<0.05 taken as statistically significant for two-tailed tests.

RESULTS

A total of 342 pediatric patients with newly diagnosed epilepsy were enrolled in the study. **Table 1;** The mean age was 9.4 years, with a slight male predominance. Patients who discontinued were slightly older (p=0.042), had a higher baseline seizure frequency (p=0.018), and exhibited higher baseline behavioral problem scores on the CBCL (p=0.035).

Table 1: Baseline Demographic and Clinical Characteristics of the Study Cohort

Characteristic	Total Cohort (N=342)	Completed Study (n=310)	Discontinued (n=32)	p-value
Age at enrollment, years (mean ± SD)	9.4 ± 3.2	9.3 ± 3.1	10.1 ± 3.5	0.042
Sex, Male, n (%)	184 (53.8%)	165 (53.2%)	19 (59.4%)	0.512
- Childhood Absence Epilepsy	68 (19.9%)	65 (21.0%)	3 (9.4%)	0.05
- Self-limited Epilepsy with Centrotemporal Spikes	94 (27.5%)	88 (28.4%)	6 (18.7%)	0.013
- Structural Focal Epilepsy	112 (32.7%)	98 (31.6%)	14 (43.8%)	0.012
- Genetic Generalized Epilepsy (other)	68 (19.9%)	59 (19.0%)	9 (28.1%)	0.01
Baseline Seizure Frequency, per month (median [IQR])	4 [2-8]	4 [2-7]	6 [3-12]	0.018
Baseline WISC-V FSIQ (mean ± SD)	101.2 ± 13.4	101.5 ± 13.1	98.4 ± 15.2	0.048
Baseline CBCL Total Problems T-score (mean ± SD)	52.1 ± 8.4	51.8 ± 8.1	54.9 ± 9.2	0.035

Table 2: There was a highly significant reduction in median monthly seizure frequency from baseline to 12 months ($p < 0.001$.
The efficacy of LEV in controlling seizures was robust. By the end of the 12-month observation period, a significant reduction in seizure frequency was observed across the cohort.

Table 3: Seizure Control Outcomes at 6 and 12 Months of Levetiracetam Therapy

Efficacy Parameter	6 Months (n=328)	12 Months (n=310)	p-value
Median Seizure Frequency (per month) [IQR]	1 [0-3]	0 [0-1]	< 0.001
≥ 50% Reduction in Seizure Frequency, n (%)	254 (77.4%)	230 (74.2%)	0.312
100% Seizure Freedom, n (%)	162 (49.4%)	181 (58.4%)	< 0.001
Time to First Seizure post-baseline, months (median)	4.2	N/A	N/A
Retention Rate on LEV Monotherapy, n (%)	328 (95.7%)	310 (90.6%)	< 0.001

Table 3: Notably, LEV therapy did not result in cognitive decline. Instead, there were statistically significant improvements in FSIQ ($p < 0.001$), Working Memory ($p < 0.001$), and Processing Speed ($p < 0.001$).

Neuropsychological assessments were utilized to determine the impact of LEV on cognitive development. The primary focus was on changes in WISC-V indices and NEPSY-II subtests from baseline to 12 months.

Table 4: Cognitive Outcomes (WISC-V and NEPSY-II) at Baseline and 12 Months

Cognitive Domain (Standard Score)	Baseline (mean ± SD)	12 Months (mean ± SD)	Mean Change (95% CI)	p-value
WISC-V Full-Scale IQ (FSIQ)	101.5 ± 13.1	103.2 ± 12.8	+1.7 (0.8 to 2.6)	< 0.001
WISC-V Verbal Comprehension	100.8 ± 14.2	101.1 ± 13.9	+0.3 (-0.5 to 1.1)	0.412
WISC-V Visual Spatial	101.2 ± 13.5	102.0 ± 13.1	+0.8 (0.1 to 1.5)	0.024
WISC-V Fluid Reasoning	100.5 ± 14.0	101.4 ± 13.6	+0.9 (0.2 to 1.6)	0.018
WISC-V Working Memory	98.4 ± 13.8	101.5 ± 13.2	+3.1 (2.2 to 4.0)	< 0.001
WISC-V Processing Speed	99.1 ± 14.5	102.8 ± 14.1	+3.7 (2.8 to 4.6)	< 0.001
NEPSY-II Attention/Executive	97.5 ± 12.4	99.2 ± 11.8	+1.7 (0.9 to 2.5)	< 0.001
NEPSY-II Memory and Learning	99.8 ± 13.1	100.5 ± 12.9	+0.7 (-0.1 to 1.5)	0.084

Table 4: While internalizing problems (anxiety/depression) remained stable, there was a highly significant worsening of externalizing problems ($p < 0.001$).

Despite the favorable cognitive profile, behavioral adverse events were a prominent finding. The CBCL was used to quantify emotional and behavioral changes.

Table 5: Behavioral Outcomes (CBCL T-scores) and Adverse Events at Baseline and 12 Months

CBCL Scale / Adverse Event	Baseline (mean ± SD)	12 Months (mean ± SD)	Mean Change (95% CI)	p-value
CBCL Internalizing Problems	51.4 ± 8.5	52.1 ± 8.8	+0.7 (-0.2 to 1.6)	0.124
CBCL Externalizing Problems	50.8 ± 7.9	54.6 ± 9.4	+3.8 (2.8 to 4.8)	< 0.001
CBCL Aggressive Behavior	51.2 ± 8.1	56.4 ± 10.2	+5.2 (4.1 to 6.3)	< 0.001
CBCL Rule-Breaking	50.5 ± 7.5	53.2 ± 8.9	+2.7 (1.8 to	< 0.001

Behavior			3.6)	
CBCL Attention Problems	54.2 ± 9.1	52.8 ± 8.7	-1.4 (-2.3 to -0.5)	0.003
Incidence of Irritability, n (%)	12 (3.5%)	68 (21.9%)	N/A	< 0.001
Incidence of Somnolence/Fatigue, n (%)	24 (7.0%)	18 (5.8%)	N/A	0.542

Table 5: Higher serum LEV levels were associated with significantly better seizure control ($p < 0.001$) and slightly better cognitive gains in working memory ($p = 0.012$).

To understand the drivers of efficacy and behavioral toxicity, a subgroup analysis was performed correlating outcomes with LEV serum trough levels and SV2A genotypes.

Table 5: Subgroup Analysis: Cognitive and Behavioral Outcomes Stratified by LEV Serum Trough Levels

Outcome Measure	**Low Level (< 30 µg/mL) (n=95)**	**Moderate Level (30-50 µg/mL) (n=142)**	**High Level (> 50 µg/mL) (n=73)**	**p-value**
Seizure Freedom at 12 mos, n (%)	38 (40.0%)	89 (62.7%)	54 (74.0%)	< 0.001
Δ WISC-V Working Memory (mean ± SD)	+2.1 ± 3.4	+3.2 ± 3.8	+3.8 ± 4.1	0.012
Δ CBCL Aggressive Behavior (mean ± SD)	+1.8 ± 4.2	+4.5 ± 5.1	+8.9 ± 6.4	< 0.001
Incidence of Severe Irritability, n (%)	8 (8.4%)	24 (16.9%)	36 (49.3%)	< 0.001
SV2A rs3766128 Minor Allele Freq, n (%)	22 (23.2%)	38 (26.8%)	24 (32.9%)	0.034

DISCUSSION

The treatment of paediatric epilepsy is a delicate balance in achieving the best seizure control whilst ensuring that the anti-seizure medications (ASMs) do not adversely affect the developing brain. Our results validate the efficacy of LEV in inducing seizure freedom and indicate a strong cognitive-sparing profile, but also a substantial risk of externalization of behavioral adverse events with clear links to both serum levels of the drug and specific polymorphisms. The seizure control results found in this study are consistent with and reinforce recent large-scale trials that have also demonstrated LEV to be a leading first-line therapy for focal and generalized epilepsies, such as the SANAD II trial.[15] Seizure freedom had increased progressively, from 6 to 12 months, which highlights the need for proper titration and the need to give enough time to achieve the best therapeutic dose in clinical practice.[16]

The neuropsychological assessments conducted with the WISC-V and NEPSY-II showed that LEV was not only able to maintain cognitive functioning but also to significantly increase Full-Scale IQ, Working Memory and Processing Speed after 12 months. It seems to be a strong support for the hypothesis that LEV is cognitively sparing.[17] LEV does not inhibit voltage-gated sodium channels, nor does it increase the effects of GABAergic inhibition in neurons, which are the mechanisms that are typically used in traditional ASMs to globally reduce neuronal excitability and thus slow down cognitive processing speed and memory consolidation, but rather it binds to the SV2A protein.[18] LEV specifically blocks pathogenic hyper-synchronization, without blocking normal low-frequency physiological neurotransmission necessary for learning and memory, caused by high-frequency neuronal firing.[19] However, it is important to recognize practice effects due to repeated testing and the prevention of subtle, subclinical seizures undoubtedly aid in optimizing neural networks.[20] Even when there are no clinical seizures, epileptiform activity has been shown to affect sleep structure and impair synaptic plasticity, especially in the hippocampus and frontal lobes.[21] We found that behaviours are more externalized, particularly aggressive behaviour and irritability, with almost one-quarter (22%) of

patients having clinically significant irritability at 12 months. This "behavioral paradox" of LEV is well documented in the literature but poorly understood in terms of its actual pathophysiological mechanisms.[22]

The authors suggest that the fast modulation of SV2A followed by changes in the release of different neurotransmitters, such as glutamate and GABA, may unselectively affect the delicate balance of its excitatory/inhibitory circuits that underlie emotional regulation.[23]

Importantly, our subgroup analysis revealed a clear exposure-response relationship for these adverse events related to behavior. Patients who had higher serum LEV trough levels (> 50 µg/mL) had significantly more severe irritability and aggression but had better seizure control. Although this pharmacogenetic discovery needs to be replicated in larger cohorts, it does point towards the possibility of using genetic tests to tailor LEV therapy to individual children to determine which ones are likely to have behavioural adverse effects before taking the treatment at all.[24]PEDiatric neurologists need to be proactive in the management of LEV therapy. The first one is the golden rule of "start low and go slow. An extended titration rate might reduce sudden changes in neurochemicals that lead to adverse behavioral events.[25]

There are several strengths of this study, including its prospective, longitudinal design; its use of comprehensive and standardized neuropsychological batteries; and the incorporation of pharmacokinetic and pharmacogenetic information. But some of the restrictions must be recognized.

CONCLUSION

Levetiracetam is an effective first-line monotherapy in the treatment of paediatric epilepsy with superior seizure control and clear cognitive-sparing effect, which helps to maintain and even improve working memory and processing speed. It has been, however, marred by a high rate of externalisation of behavioural adverse events, especially irritability and aggression, which are highly dose dependent. Slow titration, regular behavioral screening, and pharmacogenetic screening should be considered to tailor therapy to the individual child and achieve optimal efficacy and tolerability, which will lead to better long-term neurodevelopmental outcomes.

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