The Association of Small-worldness (Node Assortativity) and Internalizing Symptoms in Pediatric Patients with Drug Resistant Epilepsy Receiving Ketogenic Diet Therapy

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Introduction

About one third of the children with epilepsy are drug-resistant epilepsy (DRE). The medical burden, high morbidity and high mortality are a significant public health issue. The ketogenic diet (KD) is an effective alternative therapy for DRE. However, there are no specific predictors for KD effectiveness except patients with glucose transporter 1 deficiency syndrome and pyruvate dehydrogenase deficiency syndrome. In this prospective study, we aimed at effects of a 12-month-lasting KD on brain connectivity, measured by functional MRI (fMRI), and its correlation with seizure reduction, patients' behavioral/mood problems and parental stress.

Methods

Children with DRE were enrolled in this single-center, prospective, cohort study from February 2018 to October 2019. All study subjects were divided into two groups: the control group and the KD group. Child Behavior Checklist (CBCL) and Parental Stress Index (PSI) were applied for parents at KD initiation and at 12 months of KD therapy to assess patients' social behavior and mood status as well as caregivers' stress. Resting- fMRI was executed at KD initiation and at 6 months of KD therapy for brain network functional analysis.

Results

22 patients diagnosed as DRE were enrolled in our study. 13 patients were in the control group, and 9 patients were in the KD group. The baseline seizure frequencies were significantly higher in the KD group, however, after 12 months of KD therapy, the seizure frequencies became comparable between the two group.

The patients with DRE receiving KDT for 12 months would improve depressive mood and present less aggressive behaviors, oppositional defiant problems and conduct problems when compared to baseline. The levels of Parental Distress, Parent-Child Dysfunctional Interaction and

Total Stress significantly declined from mother's report after 12 months of KD therapy. (Table 1 and Table 2)

As for brain network analysis, the net assortativity difference, ΔAssortativity, showed positively correlated with aggressive behavior on syndrome scales and conduct problems scores on DSM-oriented scales for KD group. The ΔAssortativity value showed negatively correlated with seizure reduction rate for KD group. (Figure 1 and Figure 2)

Child behavior checklist (CBCL)

	Intragroup comparison		Intergroup comparison	
	KDT (T0 v.s. T1)	CTL (T0 v.s. T1)	T0 (KDT v.s. CTL)	T1 (KDT v.s. CTL)
Mother report				
Syndrome Scale Scores				
Anxious/Depressed	p = 0.172	p = 0.465	**p = 0.042***	p = 0.285
Withdrawn/Depressed	**p = 0.042***	p = 0.891	**p = 0.016***	p = 0.086
Somatic Complaints	p = 0.075	**p = 0.043***	p = 0.222	p = 0.317
Social Problems	p = 0.674	p = 0.753	**p = 0.014***	**p = 0.007****
Thought Problems	p = 0.799	p = 0.496	p = 0.100	p = 0.071
Attention Problems	p = 0.357	p = 0.271	**p = 0.028***	**p = 0.018***
Rule-Breaking Behavior	p = 0.344	p = 0.752	p = 0.923	p = 1.000
Aggressive Behavior	p = 0.271	p = 0.865	**p = 0.028***	p = 0.240
DSM-Oriented Scales				
Depressive Problems	**p = 0.041***	p = 0.232	**p = 0.023***	p = 0.263
Anxiety Problems	p = 0.225	p = 0.400	**p = 0.033***	p = 0.137
Somatic Problems	p = 0.225	p = 0.141	p = 0.507	p = 0.957
ADHD	p = 0.271	**p = 0.046***	p = 0.190	**p = 0.040***
Oppositional Defiant Problems	**p = 0.046***	p = 0.864	p = 0.145	p = 0.807
Conduct Problems	p = 0.672	p = 0.611	**p = 0.042***	p = 0.373
Father report				
Syndrome Scale Scores				
Anxious/Depressed	p = 0.273	p = 0.655	**p = 0.037***	p = 0.882
Withdrawn/Depressed	p = 0.058	p = 0.461	p = 0.322	p = 0.954
Somatic Complaints	p = 0.180	p = 0.357	p = 0.624	p = 0.900
Social Problems	p = 0.416	p = 0.588	**p = 0.040***	**p = 0.040***
Thought Problems	p = 0.715	p = 0.785	p = 0.767	p = 0.516
Attention Problems	p = 0.128	p = 0.779	p = 0.164	p = 0.416
Rule-Breaking Behavior	p = 0.498	p = 1.000	p = 0.952	p = 0.903
Aggressive Behavior	**p = 0.041***	p = 1.000	p = 0.080	p = 0.408
DSM-Oriented Scales				
Depressive Problems	**p = 0.027***	p = 0.465	p = 0.221	p = 0.485
Anxiety Problems	p = 0.140	p = 1.000	**p = 0.032***	p = 0.245
Somatic Problems	p = 0.317	p = 0.655	p = 0.458	p = 0.234
ADHD	p = 0.144	p = 0.078	p = 0.295	p = 0.640
Oppositional Defiant Problems	p = 0.285	p = 0.786	p = 0.638	p = 0.516
Conduct Problems	**p = 0.042***	p = 1.000	p = 0.499	p = 0.118

T0: Baseline; T1: 12 months; m: Mean; SD: Standard deviation; CBCL: Child behavior checklist; ADHD: Attention deficit/hyperactivity disorder
Mother report: KDT (n=8), CTL (n=7); Father report: KDT (n=7), CTL (n=8)
Comparison of T0 and T1, Wilcoxon Signed Ranks Test
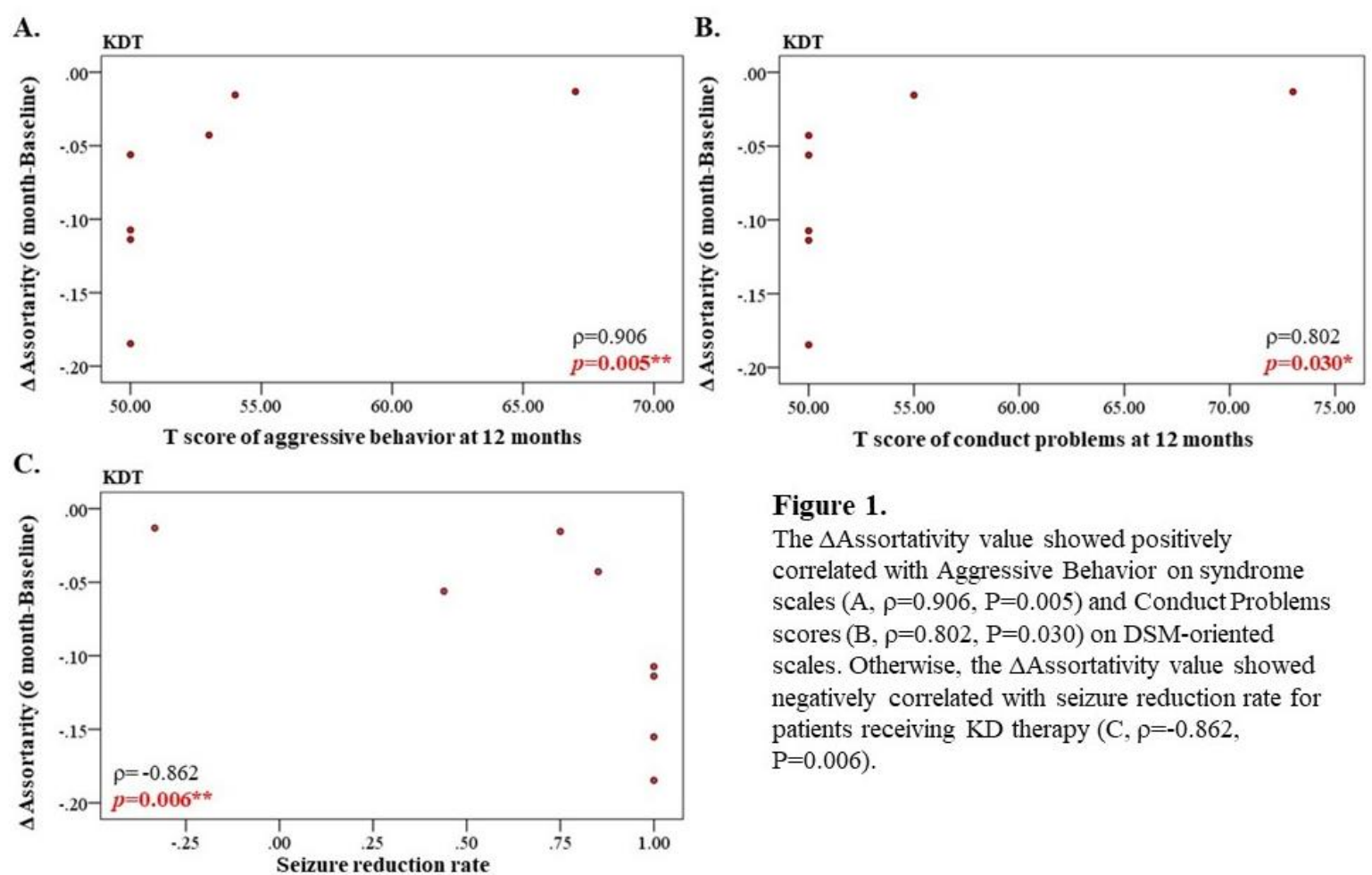Comparison of KDT group and control group at 12 months, Mann-Whitney Test

Table 1.
The subscales showed significantly lower after KDT with comparison to baseline scores by mother's report (Withdrawn/Depressed, Depressive Problems and Oppositional Defiant Problems) and father's report (Aggressive Behavior, Depressive Problems and Conduct Problem) (all p value <0.05).

Parental stress index (PSI)

	Intragroup comparison		Intergroup comparison	
	KDT (T0 v.s. T1)	CTL (T0 v.s. T1)	T0 (KDT v.s. CTL)	T1 (KDT v.s. CTL)
Mother report				
PD	**p = 0.035***	p = 0.058	p = 0.838	p = 0.805
P-CDI	**p = 0.017***	p = 0.812	p = 0.653	p = 0.190
DC	p = 0.286	p = 0.092	p = 0.870	p = 0.190
TS	**p = 0.008****	p = 0.173	p = 0.624	p = 0.220
Father report				
PD	p = 0.397	p = 1.000	p = 0.958	p = 0.088
P-CDI	p = 0.733	p = 0.080	p = 0.524	p = 0.184
DC	p = 0.735	p = 0.310	p = 0.559	p = 0.124
TS	p = 0.499	p = 0.499	p = 0.633	**p = 0.034***

T0: Baseline; T1: 12 months; m: Mean; SD: Standard deviation; PSI: Parenting stress index; PD: Parental distress; P-CDI: Parent–child dysfunctional interaction; DC: Difficult Child; TS: Total Stress
Mother report: KDT (n=9), CTL (n=10); Father report: KDT (n=7), CTL (n=9)
Comparison of T0 and T1, Wilcoxon Signed Ranks Test
Comparison of KDT group and control group at 12 months, Mann-Whitney Test
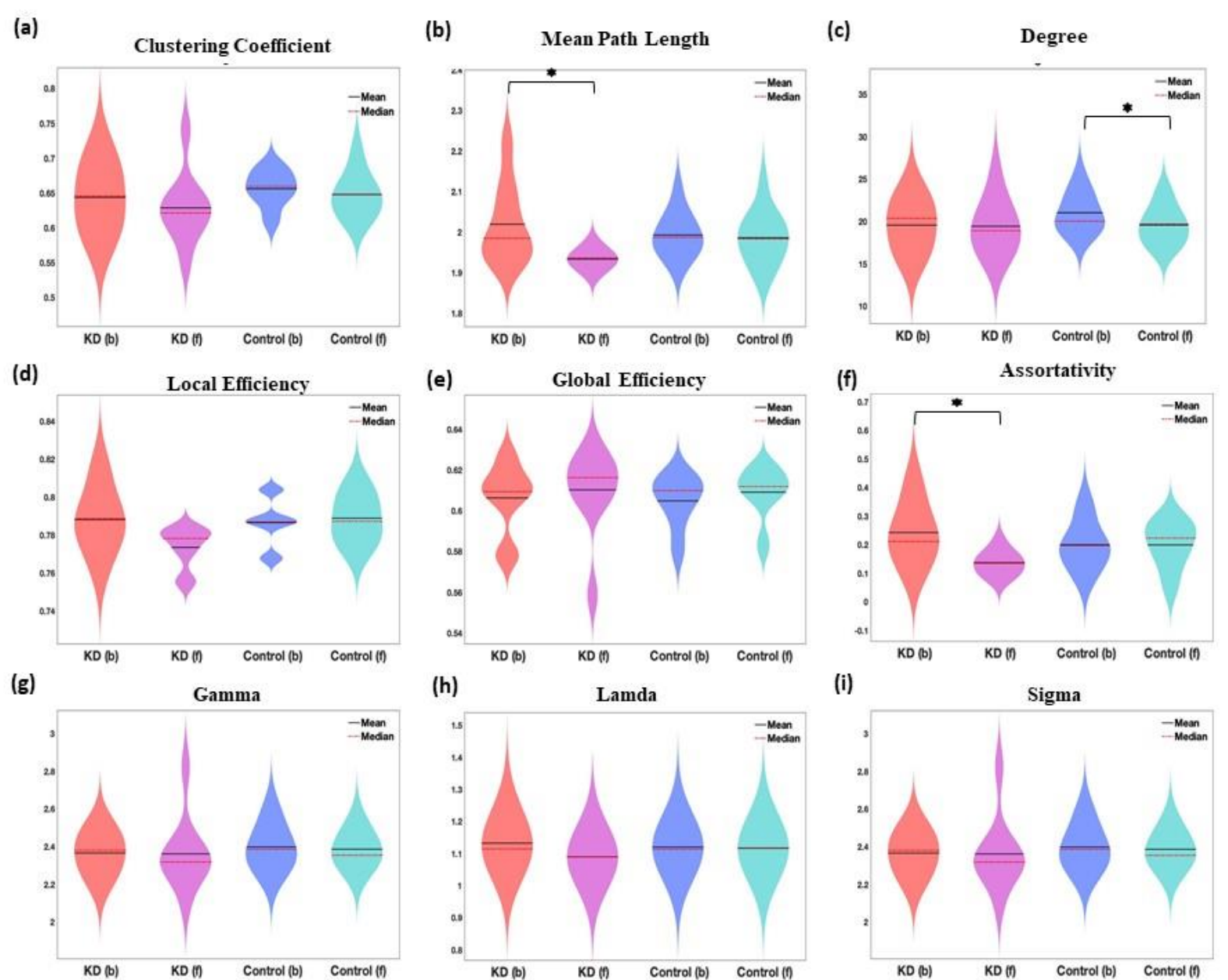
Table 2.
The levels of Parental Distress, Parent-Child Dysfunctional Interaction and Total Stress were found in decline trend from mother's report after 12 months of KD therapy with statistical significance (p value <0.05).

Figure 1.
The ΔAssortativity value showed positively correlated with Aggressive Behavior on syndrome scales (A, ρ=0.906, P=0.005) and Conduct Problems scores (B, ρ=0.802, P=0.030) on DSM-oriented scales. Otherwise, the ΔAssortativity value showed negatively correlated with seizure reduction rate for patients receiving KD therapy (C, ρ=-0.862, P=0.006).

Figure 2.
The KD (f, after) compared with the KD (b, before) showed significantly decreased value of Mean path length and ΔAssortativity.
The Control (f) compared with the Control (b) showed significantly decreased Degree.

Conclusions

12-month of KD therapy ameliorated seizure frequencies effectively. KD therapy improve depressive mood, aggressive behaviors, ODD problems, and conduct problems in patients with DRE. The parental stress was also declined after seizures being well controlled. Our study also disclosed that the lower ΔAssortativity value, the better behaviors and seizure reduction rate. The ΔAssortativity value in fMRI may play a crucial role as a predictor for KD effectiveness.