



## Vagus nerve stimulation for 6- to 12-year-old children with refractory epilepsy: Impact on seizure frequency and parenting stress index

Hueng-Chuen Fan<sup>a</sup>, Ting-Rong Hsu<sup>b,c</sup>, Kai-Ping Chang<sup>b,c</sup>, Shyi-Jou Chen<sup>d</sup>, Jeng-Dau Tsai<sup>e,\*</sup>, on behalf of the VNS TCNS<sup>f</sup>

<sup>a</sup> Department of Pediatrics, Tungs' Taichung Metroharbor Hospital, Wuchi, Taichung, Taiwan

<sup>b</sup> Department of Pediatrics, Taipei Veterans General Hospital, Taiwan

<sup>c</sup> Faculty of Medicine, National Yang-Ming University, Taiwan

<sup>d</sup> Department of Pediatrics, Tri-Service General Hospital, Taiwan

<sup>e</sup> School of Medicine and Department of Pediatrics, Chung Shan Medical University and Hospital, Taichung, Taiwan

<sup>f</sup> Vagus Nerve Stimulation Study Group of Taiwan Child Neurology Society, Taiwan

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### ABSTRACT

**Objectives:** Refractory epilepsy (RE) is frequently associated with neuropsychological impairment in children and may disrupt their social development. Vagus nerve stimulation (VNS) had been reported to have beneficial effects on behavioral outcomes. The aim of this study was to compare Parenting Stress Index (PSI) scores before and after VNS device implantation in children with RE, especially those who experienced seizure frequency reduction.

**Methods:** We conducted a one-group pretest–posttest study in school age children with RE. Seizure frequency and PSI were recorded at 12 months after VNS device implantation.

**Results:** Treatment with VNS was significantly associated with reduced seizure frequency and parental stress as measured by PSI. Factors contributing to seizure frequency included idiopathic/cryptogenic etiology and neurobehavioral comorbidities. In children with reduced seizure frequency, statistically significant improvements in the child domain of the PSI on the subscales of mood and reinforces parent were found. In the parent domain, the scores for social isolation were reduced.

**Conclusions:** Treatment with VNS was significantly associated with reduced seizure frequency and improved PSI scores, especially within the child domain on the mood and reinforces parent subscales. These findings suggest that VNS reduced not only seizure frequency but also the psychological burden on children with RE.

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### 1. Introduction

Refractory epilepsy (RE) in children is frequently associated with neuropsychological impairment, especially when it disrupts a developmental period essential to their intellectual and social maturation [1]. The presence of neuropsychological impairment tends to be the most important variable affecting quality of life in patients with RE, even more so than seizure frequency [2]. Children with RE often concomitantly present with behavior, mood, and sleep disorders. These comorbidities, alone or in combination with RE, may restrict the daily life of these children and their parents [3] and impose a significant financial and stress burden on the main caregivers [4].

Previous studies evaluating the outcome of vagus nerve stimulation (VNS) in pediatric patients with RE have shown this treatment

to be effective [5,6]. Significant reduction of seizure frequency as well as beneficial effects on behavioral outcomes and quality of life were reported [7,8]. Most studies have observed stable cognitive function during the course of VNS treatment, and some have even reported additional beneficial effects of VNS on children with RE [9,10]. The use of VNS improved general mood and reduced feelings of depression, irrespective of whether seizure frequency decreased [11, 12]. Therefore, early and more effective seizure control may improve cognitive outcomes and quality of life in children [13]. Children with RE may also be burdened with intellectual disability (ID) and consequent school life adaptation problems. The entrance of school and change of life pattern may lead to face problems and psychological stress.

To date, only a limited number of studies have included psychological assessment of cognitive function or stress levels of caregivers to investigate whether the stress in the parent–child relationship was reduced, especially after the entrance of school. Therefore, the aim of this study focused on elementary school age children, investigating the Parenting Stress Index (PSI) of 6- to 12-year-old children undergoing VNS treatment.

\* Corresponding author at: Department of Pediatrics, Chung Shan Medical University Hospital, #110, Section 1, Jianguo North Road, Taichung 402, Taiwan.

E-mail address: [fernand.tsai@msa.hinet.net](mailto:fernand.tsai@msa.hinet.net) (J.-D. Tsai).

## 2. Methods

This was a prospective, open-label, multi-institutional, consecutive cohort study involving 13 medical centers in Taiwan during 2008 to 2014. Criteria for the selection and exclusion of patients, acquisition of informed consent, procedures of implanting device, pre- and posttreatment assessment, and the protocol of the trial were set up by the Taiwan Child Neurology Society VNS study group and described in the following sections.

Selection criteria included a medical diagnosis of RE, age between 6 and 12 years, and a stable neurological condition without acute illness. Exclusion criteria included progressive neurological conditions and/or unstable illness of any other type. All pediatric patients with medically intractable seizures were defined as having RE if they were taking two or more antiepileptic drugs and had been previously followed up for at least 2 years. The patients with RE that underwent VNS device implantation had their detailed clinical histories and neuropsychology assessment taken.

Baseline seizure frequency was recorded, and Intelligence Quotient (IQ) and PSI tests were administered before the VNS devices were implanted. Follow-up examinations for each patient were taken at 12 months after VNS device implantation. For seizure frequency, patients were assigned to groups I to IV according to the number of seizures per week. Groups I through IV experienced >35, 14–35, 1–13, and <1 seizure per week, respectively. Seizure frequency reduction was defined as moving from a group with higher seizure frequency to another with a lower one. The study was approved by the respective institutional review board at each research center. Informed consent was acquired from the caregivers prior to collection of patient data as required in the protocol.

The neuropsychology assessment was performed by a pediatric psychologist using the Wechsler Intelligence Scale for Children (4th Edition) and the PSI (3rd Edition). The PSI measures the level of stress in the parent–child interaction [14,15]. It includes scores on 13 subscales describing aspects of the Child and Parent domains; the sum of both domains provides a measure of the total stress in the parent–child interaction. The Child domain examines characteristics of the child, and its subscales include Distractibility/Hyperactivity, Adaptability, Reinforces Parent, Demandingness, Mood, and Acceptability. The Parent domain examines how parents perceive themselves in their role, as well as the impact of parenting on their life. This domain includes the subscales of Competence, Isolation, Attachment, Health, Role Restriction, and Spouse/Parenting Partner Relationship.

## 3. Results

Our sample group comprised 26 pediatric patients (16 male, 10 female) aged 6–12 years undergoing VNS device implantation. Medical data included seizure frequency, etiologies, and neurobehavioral comorbidities. All patients completed psychological assessments (IQ and PSI) preimplantation and postimplantation. The seizure frequency of the subjects varied widely. Therefore we recorded seizure frequency weekly to minimize the seizure frequency range, which shortened the X axis range. Patients were grouped according to seizure frequency before VNS device implantation as follows: 12 (46.2%) in group I (>35/week), 11 (42.3%) in group II (14–35/week), and 3 (11.5%) in group III (1–13/week) (Table 1). Etiologies included central nerve system infection in 5 (19.2%), brain malformation in 4 (15.4%), hypoxic–ischemic encephalopathy in 2 (7.7%), neurocutaneous syndrome in 2 (7.1%), and periventricular leukomalacia in 1 (3.8%). Of seizure types, 24 (92.3%) had 2 or more seizure types, and 2 (7.7%) had complex partial seizures. Of the 26 patients, 18 (69.2%) had neurobehavioral comorbidities, including intellectual disability in 20 (76.9%), autistic spectrum disorder in 5 (19.2%), attention-deficit hyperactivity disorder in 2 (7.7%), and cerebral palsy in 2 (7.7%).

**Table 1**

Demographic data of school age patients with refractory epilepsy who underwent VNS device implantation. N = 26.

Parameter	Variable	N (%)
Gender	Male	16 (61.5)
	Female	10 (38.5)
Age (years)	6–9	7 (27.0)
	9–12	19 (63.0)
	I (>35)	12 (46.2)
Group of seizures frequency (average/per week)	II (14–35)	11 (42.3)
	III (1–13)	3 (11.5)
	IV (<1)	0
	Etiology	Symptomatic
Etiology	CNS infection	5 (19.2)
	Brain malformation	4 (15.4)
	HIE	2 (7.7)
	Neurocutaneous syndrome	2 (7.7)
	PVL	1 (3.8)
	Idiopathic/Cryptogenic	12 (46.2)
	Seizure type	CPS
Neurobehavioral comorbidities	SPS	0
	Generalized seizure	0
	≥2 pattern	24 (92.3%)
	ID	20 (76.9)
Neurobehavioral comorbidities	ASD	5 (19.2)
	ADHD	2 (7.7)
	Cerebral palsy	2 (7.7)
	None	8 (30.8)

VNS: Vagus nervous stimulation; CNS: central nerve system; HIE: hypoxic–ischemic encephalopathy; PVL: periventricular leukomalacia; CPS: complex partial seizure; SPS: simple partial seizure; intellectual disability: ID; Autistic spectrum disorder: ASD; Attention-deficit hyperactivity disorder: ADHD. Generalized seizures included tonic, clonic, tonic–clonic and myoclonic seizures.

As shown in Table 2 and Fig. 1a, VNS device implantation led to a significant change in the seizure frequency distribution. Before implantation, 12 (46.2%) and 14 (53.8%) patients reported >35 and ≤35 seizures per week, respectively. After implantation, the respective groups comprised 2 (7.7%) and 24 (92.3%) patients ( $P < 0.01$ ). As shown in Fig. 1b, follow-up of the patients with reduced seizure frequency revealed a significant reduction in their total PSI score ( $P < 0.01$ ). The distribution of seizure frequency groups recorded after implantation showed 13 (50.5%) patients in group II followed by 10 (38.5%) in group I (Fig. 2). Eleven of the 26 (42.3%) had more than 50% seizure reduction. The distribution of seizure types recorded after implantation showed 13 (50.0%) had 2 or more seizure types; 8 (30.8%) had simple partial

**Table 2**

Outcomes of seizures frequency reduction, IQ test and PSI in school age patients with VNS device implantation. N = 26.

Parameter	Pre-VNS	Post-VNS	P-value
Seizures frequency			
Distribution (average/per week)			
>35	12 (46.2)	2 (7.7)	<0.01**
≤35	14 (53.8)	24 (92.3)	
Gender			
Male	32.5 (1–600)	16.5 (1–180)	0.051
Female	33 (1.5–230)	12.5 (0–130)	0.112
Etiology			
Symptomatic	18 (1.5–240)	9 (0–130)	0.132
Idiopathic/Cryptogenic	70 (1–600)	17.5 (1–180)	<0.05*
Neurobehavioral comorbidities			
Yes	25 (1–240)	16 (0–130)	<0.05*
No	45.5 (4.5–600)	13.5 (3–180)	0.109
IQ test			
All	41 (40–52)	42 (40–59)	0.299
PSI			
Child domain	135 (124–153)	129 (113–142)	0.034
Parents domain	146 (132–169)	144 (130–165)	0.236

Seizures frequency: average/per week; Data are shown as patient numbers and Median (range); VNS: Vagus nerve stimulation; IQ: Intelligence Quotient. PSI: Parenting stress index. \*: Statistical significance. \*: <0.05; \*\*: <0.01.

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