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Review Article

Vagal Nerve Stimulation in Developmental Encephalopathies and Epilepsy: A Narrative Review

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Abstract

Purpose: Developmental epileptic encephalopathies (DEE) are a group of conditions featuring drug-resistant epilepsies and a large spectrum of comorbidities, which result in an enormous psychosocial burden. In the last decade, the use of vagus nerve stimulation (VNS) as adjuvant therapy for seizure control has been implemented. The purpose of this article is to collect evidence on the effectiveness of the use of VNS as adjuvant therapy in DEE

Methods: PUBMED, EMBASE, and Cochrane databases were searched through April 2022 for original articles on VNS in DEE, without restriction on language or year of publication.

Results: A total of 251 articles. All retrospective, including the following pathologies: CDKL5, Rett, tuberous sclerosis, progressive myoclonic epilepsies, non-ketotic hyperglycinemia, Berardinelli-Seip syndrome, Gaucher III and Unverricht Lundborg were retrieved. These articles reported on a total of 116 patients, of which 12% presented an improvement of seizures between 80-100 %, 62% between 50-79%, 19% less than 50%. And only 7% showed no improvement. Additionally, improvement of behavior, alertness, concentration, quality of life, and communication skills were reported.

Conclusion: Of the total 116 patients, seizure reduction of more than 50% respect to the baseline was reported in 73% of them, associated with improvement of alertness, behavior, and neurodevelopment. Although VNS had mainly palliative effects our findings may suggest a favorable impact of this non-pharmacological therapy in this very difficult-to-treat group of epilepsies. Prospective studies are required to evaluate not only the reduction in seizure frequency but also these other qualities of life parameters.

INTRODUCTION

Epilepsy is a common neurological disorder that affects approximately 50 million people in the world, and it is often associated with multiple comorbidities and high psychosocial impact. In about one third of patients, their seizures are not completely controlled despite therapeutic efforts with several antiseizure medications (ASM). According to the international league against epilepsy (ILAE), these patients can be defined drug-refractory when their seizures persist after having tried at least two ASMs, indicated for their type of epilepsy and at adequate doses [1].

In the pediatric age, a large group of epilepsies. i.e., Developmental Epileptic Encephalopathies (DEE) features drug-resistant seizures and a spectrum of intellectual disabilities, ranging from mild to very severe. These are a heterogeneous group of diseases in which the presence of interictal epileptiform activity by itself contributes to the cognitive deterioration of patients. However, recent advances suggest that the encephalopathic picture may be related to other factors of the etiology, beside epileptiform EEG activity [2]. An epileptic encephalopathy can be considered as a triad of features: seizure, epileptiform activity on EEG, and adverse effects on development, cognition, and often behavior [3].

This group of conditions is often refractory to multiple pharmacological and non-pharmacological strategies, including dietary treatments such as the ketogenic diet. In 1997, the US Food and Drug Administration (FDA) approved VNS as an adjunctive treatment for patients with refractory epilepsy who were poor not candidates for epilepsy surgery or who had not been controlled by various therapeutic approaches such as the ketogenic diet or multiple ASM. The beneficial effect of VNS is hypothesized to be related to its ability to reduce cerebral perfusion, including areas such as the thalamus, hypothalamus, hippocampus, and amygdala, in addition to other pathophysiological hypotheses that relate to

the release of cerebral NA, changes in the solitary nucleus or the modulation of the reticular activation, as a possible mechanism of action [4]. In addition to its antiepileptic effect, VNS treatment has been associated with improved psychosocial functioning such as mood and alertness, which could be promising for these patients.

In the cases of patients with DEE, the presence of genetic etiology could, in a large proportion of cases, exclude them from resective surgical treatment. It is in these cases that palliative therapy with stimulation of the vagus nerve could have a relevant role in seizure control and possibly in improving neuropsychiatric comorbidities.

METHODOLOGY

Objective

Our objective was to perform a narrative review of the literature to collect data in various DEE, in whom VNS was employed as adjuvant therapy to describe primarily the effect of this treatment on seizure control. In addition, we aimed to collect information also on neuropsychiatric and quality of life variables, such as improvement in a behavior pattern, alertness, and self-injury.

Eligibility criteria and source of information

This literature review used methods published in the PRISMA 2020 statement [5], whose participants were patients with a diagnosis of some DEE in whom VNS had been used as coadjuvant management.

A search was performed in PubMed, EMBASE, SCIELO, and Cochrane library.

VNS responders were defined as those who presented a reduction of more than 50% in seizure frequency compared to preoperative baseline. Seizure freedom was defined as seizure freedom for at least 6 months; additional measures that were investigated were decrease in seizure intensity and duration.

Data collection

Search criteria were established in the form of free text and indexed terms. We used following terms: Epilepsy, Developmental encephalopathies and epilepsy, Genetic epilepsies, VNS therapy. A gray literature search was also performed on the pages of the National Technical Information Service (NTIS) and the European Association for Grey Literature Exploitation (EAGLE), in which no relevant information was found. Additionally, cross-references were searched in articles found, by manual snowball search.

Synthesis of the results

The articles were evaluated by title and abstract by two reviewers independently. In case of disagreement, analysis by a third reviewer was considered. Filters were not set by year of publication or by language, only human studies were searched. Duplicate articles and Dravet syndrome, which has a meta-analysis that covers the topic in question, were eliminated (6). A minimum of 3 months of postoperative follow-up was required for inclusion. References from all selected papers were further examined for additional suitable studies and to identify a possible patient or paper duplication. Overall, 133 studies met our initial inclusion criteria before we applied the following exclusion criteria: 1) review only or registry survey, 2) data fully redundant with those in another report, 3) Studies made in murine, 4) did not include patients with DEE. In total, 71 articles remained after applying all exclusion criteria.

The articles eligible for full-text reading were filtered according to the type of study and finally, the useful articles for qualitative analysis were found. The DEE that we investigated were selected because the data in other genetic DEE were very few. Finally, 25 studies were included, all retrospective in nature (Figure 1).

RESULTS

CDKL5 [6-9]

Mutations in the X-linked cyclin-dependent gene 5 (CDKL5) (formerly known as STK9, serine/threonine kinase, now known as CDKL5 deficiency disorder) are responsible for a severe encephalopathy with X-linked infantile spasms. It is characterized by intellectual disability, early-onset epileptic seizures, usually refractory to treatment and behavioral alterations [10]. Development is independent of seizures, however, seizure activity can worsen the developmental delay, and thus an effective treatment to reduce the seizure burden is needed.

There are 42 patients reported in the literature implanted with VNS, of which there is complete information on 40.

In Lim's series *et al. [7], 222 patients with CDKL5 were followed up, of whom 38 had previous or current use of VNS, with complete information on 36. The mean age at implantation was 4.9 years (range 1.3- 20 years); Improvements in seizure activity after implantation of VNS were reported for 69% of individuals (25/36). These improvements included reductions in the duration (18/25,*

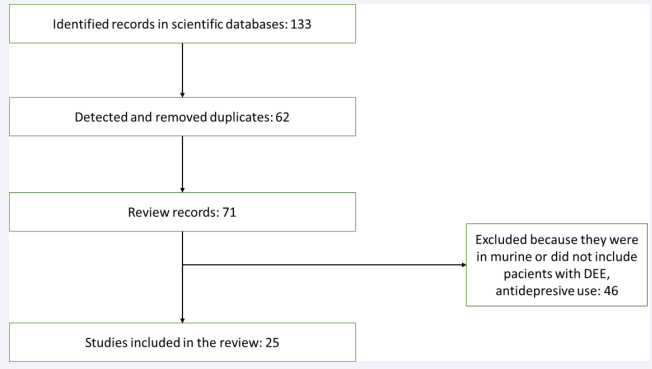

Figure 1 Flowchart of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) search statement.

72%), frequency (17/25, 68%,), and intensity (15/25, 60%,) of seizures. The median duration of VNS use before any seizure improvement was 73 days (range: 1 day – 24 months), No seizure-free patients or there any changes in medications during the follow-up were reported. The median current seizure frequency was 1.7 (range 0-70) episodes per day among individuals who never used the VNS, 3 (range 0-12) for those currently using the VNS and 2.6 (range 1-15) for those who had ceased using the VNS. Compared to those who never used the VNS, the seizure rates appeared similar in those currently using the VNS.

Additionally, they showed improvements of behavior part in 24% of individuals, improvement in alertness in 19%, and improvement in mood in 8%.

Baba et al. [6], presented a patient with seizure that began at 6 months of life, with no improvement despite the use of 7 antiepileptic drugs, ACTH, and ketogenic diet; she was implanted with VNS at the age of 6. After VNS, seizure frequency improved, from daily to weekly seizures. Additionally, an amelioration of alertness, behavior, neurodevelopmental status and equality of life was reported, by using the "Improvement of Clinical Global Impression" and quality of life scales.

Kobayashi et al. [9], recruited 29 patients with pathogenic or likely pathogenic CDKL5 variants from a cohort of 1.100 patients, in whom VNS was performed in three patients; however, none of these patients showed seizure reduction.

RETT SYNDROME [11,12]

Rett syndrome (RTT), described in 1966 by Andreas Rett, and clinically defined by Bengt Hagbergin in 1983, is a neurodevelopmental disorder that affects almost exclusively females, with a clinical course characterized by regression of previously acquired abilities after a normal development.- Features of Rett syndrome include slow head growth, gait abnormalities, loss of purposeful movements of the hands, often replaced by repetitive stereotypic movements, loss of speech and breathing abnormalities, autism spectrum disorder, respiratory disorders, behavior and epilepsy in 50-90% of cases. The syndrome is mainly caused by mutations in the MECP2 gene located on the X chromosome, which encodes methyl-binding protein 2.CpG (MeCP2), a basic nuclear protein highly expressed in the brain [13].

A total of 8 patients have been reported, 7 of which were reported by Wilfong *et al. [11],* with refractory epilepsy. In these subjects, VNS was implanted between the age of 1-14 years (mean age of 9), with an average duration of epilepsy of 6 years and an average frequency of seizures per month of 150 (range 12-3600); the mean follow-up was 12 months (3-30). It was shown that 85% (6/7) had >50% seizure reduction, and 57% (4/7) had >90% seizure reduction at 12-month follow-up. They also reported that the duration of the seizures and the postictal phase was shorter in 3 out of 7 patients (42%).

Caregivers reported improvements in alertness in all patients, with no changes in mood or communication skills.

Zamponi et al. [12], reported a patient with infantile spasms and drop attacks, with a pre-implantation seizure frequency of 90 per month; she was implanted at age 5 years and after a 12 months follow-up, seizures were reduced by approximately 50%.

TUBEROUS SCLEROSIS COMPLEX [14-20]

Tuberous sclerosis complex(TSC) is a rare, autosomal dominant genetic disease with variable expressivity, caused by a mutation in the TSC1 or TSC2 genes and resulting hyperactivity of the mammal target protein rapamycin (mTOR, for its acronym in English). A multisystem involvement, with renal, pulmonary impairment, skin disorders, epilepsy and cognitive and behavioral alterations including autism spectrum disorders, has been reported in 79-90 % of cases, with onset between 3-8 months. Seizure can be refractory to ASM in up to 80% of cases [21]. Pharmacological treatment strategies vary from preventive therapies (EPISTOP trial [22]), conventional pharmacological therapies, Everolimus, ketogenic diet, and resective surgery, however, in a proportion of patients, these therapies are not effective or not tolerated and VNS can be a possible palliative alternative.

It is one of the most studied entities with the use of VNS as adjuvant treatment, in total there have been reports of 51 patients.

Elliott et al. [14], conducted a study on 19 patients diagnosed with TSC, of which 12 were implanted only with VNS, whereas in the other 7 a surgical management (focal seizure resection, corpus callosotomy) was combined with VNS. The 12 patients with VNS only had a mean age at implantation of 16.2 years, mean age of 1.6 years for seizure onset, a mean frequency of 6 seizures per day, and 4 of the 12 had failed treatment with the ketogenic diet. One patient withdrew due to a loss of data during follow-up. They used the modified Engel scale and the scale proposed by McHugh, showing a reduction of more than 50% in 9/11 (82%), corresponding to class III or class II, according to the Engel and Mc Hugh scale, respectively. In the behavioral part, improvement in development and alertness was reported in 2/11 patients (18%) and one adolescent presented improvement in behavior as indicated by caregivers.

Additionally in 2011, Elliot et al. [20], carried out a series of 141 patients with refractory epilepsy which were managed with VNS, of which 8 had TSC as the underlying pathology, with an average implantation age of 11.1 years. The mean age of seizures of 2.8 years and the duration of epilepsy of 8.4 years before VNS treatment. The median weekly ictal frequency was 10 seizures. 42 patients had an 80-100% improvement in seizure frequency (McHuges Class I) and 42 had an improvement between 50-79% (Class II), with 13% of patients (13) who did not present any improvement. There were no significant differences in the number of antiepileptic drugs taken before and after VNS.

Grioni et al. [17], reported the results obtained in 4 patients, implanted at the mean age of 7 years (range, 3 - 14 years), with a mean follow-up of 7 years (range, 4 - 12 years). At the last follow-

up, all but 1 patient reached class IA (McHugh). Overwater [18] made follow-up with patients with TSC to see the response to different AED, including one patient with VNS but did not cause seizure reduction. Colicchio et al. [19], studied 53 patients (33 M, 20 F) of whom 3 had a diagnosis of SCT. In the follow-up, which ranged from 1 to 15 years, all had a good response to VNS stimulation; actually, they found that lesional etiologies had a statistically significant higher percentage of responders versus nonlesional etiology.

The study of Major et al. [15], included 16 patients, with a mean age at seizures onset of around 1 year, whose mean age of implantation was 15 years (range: 2–44) and the average duration of follow-up on VNS was 4 years (range: 0.5–8.6),using the Mc Hugh scale to assess seizure improvement. Outcome was classified as Class I (>80% reduction in seizure frequency) in three (3) patients (19%), Class II (50-79% reduction in frequency) in 5 patients (31%), Class III (<50% reduction) in 2 (13%), class IV (magnet benefit) in 1 (6%), and class V (no improvement) in 5 patients (31%). They found no relationship between the type of mutation and seizure control with VNS. Regarding cognition and behavior, improvement was evidenced in 5/16 (31%) patients.

Parain et al. [16], performed a multicenter study with 10 patients, whose average age of implantation was 13 years (Range 7-20 years), with an average of 7 seizures per day. 9 patients had a reduction of more than 50% of seizures, 4 had a reduction of more than 90% and one patient had no seizure improvement after the implantation of the VNS, without reporting seizure-free patients Caregivers reported improvements in alertness in 3 patients, without performing objective tests to validate this change and one patient had an improvement of more than 80% in his self-injurious behaviors.

PROGRESSIVE MYOCLONIC EPILEPSIES

Progressive myoclonic epilepsies (PME) are a group of rare clinically and genetically heterogeneous disorders, which generally have onset in late childhood or adolescence, unlike other epileptic encephalopathies where their onset is in early childhood.

In their clinical course they present refractory myoclonic seizures, associated usually with types of seizures; in some of these conditions, status epilepticus is a common feature, requiring management in intensive care unit. These disorders can be associated with different degrees of cognitive and cerebellar compromise, and with other comorbidities, depending on the type of progressive myoclonic epilepsy. The treatment is symptomatic and it aims to seizure control; in some of these disorders' palliative, support, and rehabilitation measures are necessary [23].

Attas et al. [24], reported the case of a 32-year-old male patient, whose seizures started at age of 7, initially atonic, followed by the appearance of generalized tonic-clonic and myoclonic seizures, which increased in severity and frequerncy up to than 8 a day. Three ASMs controlled seizure frequency poorly, so he was implanted with VNS. At 3 months follow-up, he reported complete control of tonic-clonic and reduction of myoclonic seizures, with no evidence of major complications or side effects.

La Fora disease [25-28]

It is an autosomal recessive PME, with onset in adolescence (between 8-19 years) caused by mutations in two genes: EPM2A located on chromosome 6q24, encoding Laforin phosphatase, and EPM2B on chromosome 6p22.3 encoding Malin ubiquitin E3 ligase; both involved in glycogen metabolism.

Mikati *et al. [25],* r reported a patient with seizure onset at age 12, who took 7 ASMs and ketogenic diet, without seizure control. The age at VNS implantation was not reported; at 12-month post-implantation follow-up, a global seizure reduction of 70% was reported (absences controlled by 100%, bilateral tonic-clonic seizures controlled by 95%, controlled myoclonic seizures in 90%, focal seizures without impaired awareness 70%).

Hajnsek *et al.* [28], reported a 19-year-old man, with disease onset at age 16, presenting with focal occipital seizures, progressive ataxia, and bilateral myoclonus of the hands that progressively evolved into generalized myoclonus, which occurred daily, without control despite the use of 5 ASMs. After VNS implantation, at one-year follow-up, no episodes of status epileptic were reported, the generalized tonic and clonic seizure and frequency of myoclonus decreased from daily to weekly, in addition cerebellar symptoms, alertness, quality of life improved. ASMs were not reduced.

Mostacci *et al*. [29], reported a 16-year-old patient, with epilepsy onset at 14 years of age. After a prolonged episode of status epilepticus lasting 66 days, he was implanted with VNS, that stopped the seizures, and led to midazolam withdrawal three days after the VNS was switched on, and withdrawal of phenobarbital and levetiracetam 14 days later.

Unverricht-Lundborg disease [26]

Unverricht-Lundborg disease (ULD) is an autosomal recessive disease that occurs in late childhood or adolescence and is related to mutations in the CTSB gene located at 21q22.3, which codes for cystatin B, a protein responsible for protecting cells from proteases.

Smith *et al.* [26], reported a 34-year-old patient with epilepsy that began around the age of 12. The diagnosis of ULD was made 12 years after seizure onset, that were poorly controlled by a polytherapy with more than 3 ASMs. Implantation of VNS at the age of 34 years was followed by completely reduction of seizures and improvement of dysarthria, tremor, and ataxia.

MERRF (Myoclonic Epilepsy with Red Ragged Fibers) [27]

MERRF is a multisystem mitochondrial disease maternally inherited and whose phenotypic features can be caused by a

mutation in more than one gene. It appears during childhood and myoclonus is the main feature.

Fujimoto *et al. [27], described a 16-year-old patient, with seizure onset at the age of 12 years, progressive cerebellar symptoms, and cognitive impairment, whose course was severe with daily seizure and 1-2 episodes of convulsive status epilepticus per year. VNS therapy led to disappearance of absences seizures and episodes of status epilepticus for 20 months, however, without improvement of cerebellar or cognitive symptoms.*

Type III Gaucher disease

This childhood-onset disease is due to a mutation in the gene GBA (beta acid glucosidase) on chromosome 1q21, and involves the storage of glucocerebroside in various organs.

Fujimoto *et al. [27], reported a woman, with seizure onset age of 13 years; with the presence of myoclonus and daily generalized tonic-clonic seizures, in whom VNS was implanted after the failure multiple ASMs, enzyme replacement, and chaperone therapy. After a 18-months follow-up, an improvement of generalized tonic-clonic seizures and of the frequency of status epilepticus was observed. However, there was no evidence of improvement in myoclonic seizures, and of cerebellar or behavioral symptoms.*

Berardinelli-Seip syndrome [30]

It is a rare metabolic disease characterized by severe generalized lipodystrophy, with total or partial absence of tissue in the subcutaneous area and other organs; Are usually associated with other growth and development disorders, and their complications include epileptic seizures and progressive neurological deterioration.

Serino *et al. [30], reported a patient with onset of seizures and developmental delay from the age of 12 months, who initially presented bilateral tonic-clonic seizures, with subsequent appearance of daily absences, palpebral myoclonus, and drop attacks, with a diagnosis of refractory epilepsy since 3 years of life. VNS implantation was carried out, with a 2-month follow-up where were found resolution of tonic seizures, a decrease in drop attacks and absences, as well as improvement in baseline neurological status (gait, speech, and social interaction), were observed.*

Nonketotic Hyperglycinemia [31,32]

It is the inborn error of metabolism characterized by deficient activity of the glycine cleavage enzyme system, resulting in the accumulation of large amounts of glycine in all body tissues, including the brain. Within its clinical spectrum, it is possible to find intractable epilepsies with alterations in neurological development.

Tsao *et al. [31], reported two patients, one implanted at six years, with a 75% reduction in seizures, in addition to improvement in the seizure duration and intensity. The other patient was implanted at 21 months, achieving seizure freedom at 15 months follow up.*

In the series by Daniele Grioni et al. [32], a 16-month-old patient was reported whose seizures started at 10 days of age, with episodes of status epilepticus and epileptic spasms, refractory several ASMs. VNS at 13 months of age achieved a 90% reduction of seizures frequency at 2 months of age, without the occurrence of episodes of status epilepticus.

Ring Chromosome 20 [33,34]

This entity is a rare condition characterized by a non-supernumerary ring chromosome 20 that replaces a normal chromosome 20, it is characterized by a peculiar epileptic phenotype (intractable focal seizures and non-convulsive status epilepticus (NCSE)), a typical EEG pattern with a background that exhibits mild slowing or bursts of sharply contoured theta activity, with a peak frequency of 5 Hz, over the fronto-temporal region, intellectual disability, and behavioral changes which manifest after seizure onset.

Chawla *et al.* [34], reported a 6-year-old patient with refractory epilepsy, microcephaly, and minor congenital anomalies. The seizure onset was from day one of life, which progressed without improvement despite pharmacological management and a ketogenic diet. VNS implantation achieved a decrease in ictal frequency with a seizure-free period of 9 months, in addition to improvement in speech, level of alertness, and social interaction as reported by the mother.

Later Parr *et al. [33],* carried out the report of a 9-year-old boy with seizure nset at 5 years of age. His seizures were not controlled despite the use of 5 ASMs, VNS implantation at 8 years of age was followed by a 6 months resolution of generalized tonic-clonic seizures, decrease of absences and atonic seizures. An increase of stimulation current was associated with non-convulsive status epilepticus, which improved when stimulation parameters returnedto the previous amperage. Additionally, they reported recovery in lost abilities, such as ambulation.

Status Epilepticus [35]

Specchio *et al.* [35], reported two patients with super refractory status epilepticus with genetically determined epilepsy, one of them was16 years old, with a confirmed mutation in ADCK3, who after 25 days of status epilepticus presented cessation of the status 7 days after implantation of VNS, with the persistence of daily myoclonic seizures that did not interfere with vital signs, however, the patient died of underlying disease 5 months after implantation.

The other patient was 6 months old at the time of implantation, with a pathogenic mutation in BRAT-1, and started with seizures from 3.5 months of age, reaching 6 AEDs without clinical response. At 6 months, he presented refractory SE, so he was implanted on day 58 of status epilepticus, and 10 days after implantation, status epilepticus ceased, with decreased ictal frequency. However, the patient died of respiratory distress syndrome.

Table 1: Demographic and seizure control characteristics.

						Seizure control % (# patients)			
Authors and publication year	**# patients**	**Type of article**	**DEE**	**Follow up**	**Age VNS placement**	**No improvement**	**<50%**	**50-79%**	**80-100%**
Baba et al (2017) Zhan et al (2018) * Kobayashi (2021)	42	R	CDKL5 mutation	19 months (14-24m)	5,4 years (4,9-9 y)	-	38 % (16)	66% (26)	-
Wilfong et al (2006) ** Zamponi et al (2011)	8	R	Rett syndrome	24 months (12-36 m)	7,3 years (2,6-9 y)	-	12% (1)	88% (7)	-
Elliot et al (2009) Major (2009) Parain (2001) Elliot et al (2011) Grionio (2019) Overwater (2015) Colicchio (2012)	51	R	Tuberous sclerosis complex	39 months (22-63 m)	13 years (11-16 y)	16% (8)	9% (5)	55% (28)	20% (10)
Al-Attas et al 2017	1	R	Progressive myoclonic epilepsy	3 months	30 years	-	-	100% (1)	-
Mikati et al (2017) Hjnsek et al (2013) ¶ Mostacci et al (2019)¶¶	3	R	Lafora disease	11 months (9-12 m)	16 years (15-17 y)	-	-	66 % (2)	33% (1)
Smith et al (2005)	1	R	Unverricht - Lundborg	6 months	34 years	-	-	-	100% (1)
Fujimoto et al (2012)	1	R	MERF	20 months	16 years	-	-	-	100% (1)
Fujimoto et al (2012)	1	R	Gaucher III	18 months	20 years	-	-	100% (1) ¶¶¶	-
Serino et al (2019)	1	R	Berardinelli - Seip Syndrome	-	3 years	-	-	100% (1)	-
Tsao CY et al (2010) Grioni et al (2010)	3	R	Non-ketotic hyperglucinemia	24 months (12-36 m)	1 year (0,5-1,1 y)	-	-	33 % (1)	66% (2)
Chawla et al (2002) Parr et al (2006) ¶¶¶¶	2	R	Ring chromosome 20	10 months (9-10 m)	7,5 years (6-9 y)	-	-	50% (1)	50% (1)
Specchio et al (2020)	2	R	Epileptic Status	-	16 years / 0.9 years	-	100% (2) ***	-	-

* In Z
han's series they reported improvement in intensity in 60% (22/38), improvement in duration in 72% (26/38)
** In the Wilfong series they reported improvement in intensity by 60%, improvement in duration by 42% (3/7)
£ Among the etiologies are alterations in migration, static encephalopathies, Lennox Gastaut syndrome, infections, metabolic syndromes, unknown cause, and tuberous sclerosis (8 patients)
¶ In the Hjnsek series, the patient presented a complete resolution of generalized tonic-clonic seizures and status epilepticus. And a decrease from daily to weekly frequency in the myoclonus.
¶¶In the Mostacci series, the patient lasted 66 days in super refractory status epilepticus, control was achieved on the third day after implantation of the VNS, without the presence of new (ES) or CTCG in the following 9 months. She had impaired alertness and died at 9 months secondary to the severity of the underlying disease.
¶¶¶ In Fujimoto's series during 20 months of follow-up, the patient managed to be free of CTCG, however, she continues to have severe myoclonus in her hands.
¶¶¶¶ In the Parr series, a resolution of CTCG was evidenced at 6 months of follow-up, with a decrease in absences and atonias.
***Patients presented a resolution of status epilepticus and decreased ictal frequency.

DISCUSSION

In the last decade, the use of VNS has become an adjuvant therapy for the management of refractory epilepsies of multiple etiologies. Although the pathophysiological mechanism for seizure control is not yet fully understood, it is known that it may involve a desynchronization of synaptic activity, decreased activity of limbic structures, and norepinephrine release, in addition to changes at the of the solitary nucleus or modulation of the reticular activating system [8].

The majority of DEE are characterized by presenting intellectual disability, early-onset epileptic seizures, generally refractory epilepsy and behavioral alterations [8]. Development is independent of seizures, however, seizure activity could worsen developmental delay; this is why that the establishment of an adequate therapeutic effort against seizures is a very important issue.

As we said DEE are characterized by high refractoriness of seizures despite adequate pharmacological and non-pharmacological management. That is the reason why VNS has been used as a therapeutic option in these patients, as an effective antiseizure treatment, without significant treatment-related side effects [8]. It is suggested that for every 10 years of active epilepsy, the rate of increase in the probability of being implanted with VNS is 25%, and some literature exposes that VNS implantation should be considered as a second-line palliative treatment strategy in children who are not candidates for resective epilepsy surgery and do not respond to or tolerate ketogenic diet.

Despite the same limited epidemiological nature of DEEs and the fact that the existing case series on the use of this device are small, our review found a total of 25 articles with retrospective characteristics, with a total of 116 patients, of which one 14% presented an improvement of the crises between 80-100%, 59% between 50-79%, 20% less than 50% and only 7% did not present improvement [Table 1] (Figure 2). The DEE with the

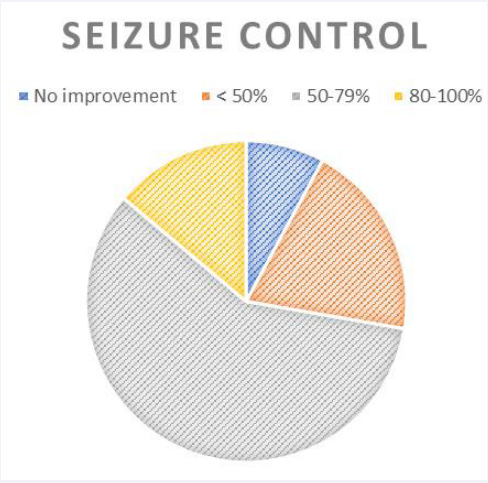

Figure 2 Percentage of seizure control in patients with DEE

most cases is tuberous sclerosis, followed by CDKL5 and Rett syndrome, with an improvement of more than 50% in 64%, 66%, and 88% respectively.

LIMITATIONS

Due to the epidemiological nature of these pathologies, the case series is limited, often collecting single cases or small case series, which may favor detection and publication bias. An additional limitation is that the results may be affected by the lack of data or standardization between the different studies, as detailed information on the effects of VNS on mood, quality of life, and qualitative aspects of seizures (duration, severity, postictal period, and intensity) often were not reported systematically and were rated on self-reported patients or caregivers, being inherently subject to errors and biases.

In the vast majority of cases, follow-up was less than two years, which may pose a bias in the long-term reporting of therapy [36].

In addition, there are potential confounding factors such as previously managed antiepileptic drugs and VNS parameters, aspects that are not mentioned in all the articles, and that can influence the results over time.

Finally, the economic analysis of the decrease in income due to seizure and/or epileptic status was not carried out, but it is an interesting aspect to consider if you consider the value of therapy.

CONCLUSIONS

Patients with DEE usually have refractory epilepsy, after having tried pharmacological and nutritional therapies without achieving seizure control. Furthermore, in most cases, there is no resective surgical option with curative intent. Therefore, we carried out this review of the literature on the use of VNS in epileptic and developmental encephalopathies, finding 25 articles with a total of 116 patients, in whom a seizure control of more than 50% was reported in 73%. of patients, evidencing in addition to seizure control, improvements in terms of alertness, behavior, and neurodevelopment, which may favor the use of this therapy as a possibility of palliative surgical management in these patients with DEE.

Prospective studies of better quality are required to evaluate not only the reduction in stroke frequency but also these other qualities of life parameters.

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