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Long-term results of vagus nerve stimulation in children with Dravet syndrome: Time-dependent, delayed antiepileptic effect

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ABSTRACT

Objective: This study aimed to assess the long-term outcomes of vagus nerve stimulation (VNS) in children with pharmaco-resistant Dravet syndrome (DS).
Methods: We enrolled 22 patients with pharmaco-resistant DS who underwent VNS implantation at Severance Children's Hospital from March 2005 to October 2020. Efficacy and tolerability were assessed at 3, 6, 12, 18, 24, 30, and 36 months after VNS implantation. Efficacy was measured as the percentage reduction in seizure frequency at each follow-up compared with the baseline (pre-implantation) values.
Results: Median patient age at VNS implantation was 10.0 years (interquartile range 7.7–13.3). The median follow-up period was 4.3 years (interquartile range 3.0–6.5) after VNS implantation. All cases were followed up for ≥2 years after VNS implantation. Three (13.6 %) patients maintained seizure freedom for ≥1 year. Among them, one achieved seizure freedom after 30 months of VNS. More than 50 % reduction in seizure frequency was observed in 36.4 % (8/22), 54.5 % (12/22), and 63.2 % (12/19) of the patients at 12, 24, and 36 months, respectively. The median percent reduction in seizure frequency was 18.8 %, 50.6 %, and 60.0 % at 12, 24, and 36 months, respectively. Compared with the baseline value, the seizure frequency was significantly lower at 24, 30, and 36 months, as well as at the longest follow-up period ($p < 0.05$, Wilcoxon signed-rank test). The symptom that was mostly associated with adverse events was hoarseness (4/22, 18.2 %); however, they had temporary or minimal effects on activities of daily living.
Conclusions: Our findings demonstrate that VNS therapy allows long-term, progressive, and time-dependent improvement in seizure control for pharmaco-resistant DS. Clinicians should be aware of the delayed VNS efficacy over the years and should encourage long-term VNS maintenance by patients.

1. Introduction

Dravet syndrome (DS), previously known as severe myoclonic epilepsy of infancy, is one of the most deleterious developmental and epileptic encephalopathies (Scheffer et al., 2017). It typically manifests as multiple types of prolonged, febrile and afebrile, seizures in the first year of life in children with normal development before seizure onset (Lagae et al., 2019). However, the affected children demonstrate cognitive and behavioral impairments from the second year of life. Most patients with DS (85 %) have a loss-of-function mutation of the *SCN1A* gene, which also supports the clinical diagnosis (Harkin et al., 2007; Liu et al., 2013; Scheffer et al., 2017). Dravet syndrome is known to be treatment-resistant despite updated therapies with clinical evidence of effectiveness, including valproic acid, topiramate, clobazam, stiripentol, cannabidiol, ketogenic diet (Chiron et al., 2000; Devinsky et al., 2017; Kossoff et al., 2018), and fenfluramine, a new drug, which significantly reduced seizures in a randomized, double-blind, placebo-controlled trial (Lagae et al., 2019); moreover, seizure freedom is rare. Vagus nerve

Abbreviations: ASM, anti-seizure medication; CTCAE, the Common Terminology Criteria for Adverse Events; DS, Dravet syndrome; IQR, interquartile range; ITT, intention-to-treat; LOCF, last observation carried forward; VNS, vagus nerve stimulation.

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stimulation (VNS), as a non-pharmacologic therapy, has also been utilized to treat patients with DS (Dibué-Adjei et al., 2017; Wirrell et al., 2017).

Given the rarity of the disease, which occurs approximately once per 16,000 births (Wu et al., 2015), the literature on VNS efficacy in patients with DS is limited (Fulton et al., 2017; Orosz et al., 2014; Zamponi et al., 2011). A recent meta-analysis identified only 13 studies with small case series and subgroups on VNS trials (Dibué-Adjei et al., 2017). Moreover, most of the studies had a rather short follow-up period. Therefore, the efficacy of VNS to treat DS needs further verification. Little has been discussed as to when the clinician can decide that VNS is ineffective for patients with DS. Thus, this study sought to assess the long-term outcomes of VNS for children with pharmaco-resistant DS. We further investigated when the seizure frequency significantly decreased, in comparison with the baseline, during the post-VNS implantation follow-up period.

2. Material and methods

2.1. Patients

We included 22 patients who were diagnosed with DS based on the International League Against Epilepsy (ILAE) and underwent implantation of a VNS device at Severance Children's Hospital from March 2005 to October 2020. We included patients aged ≤18 years at the time of VNS device implantation and excluded patients who underwent additional brain surgery during the post-implantation follow-up period. None of the patients were lost to follow-up after VNS implantation. Outpatient visits were regularly performed at 3, 6, 12, 18, 24, 30, and 36 months after VNS implantation to evaluate the efficacy and incidence of adverse events. At each visit, medical records regarding pre- and post-VNS therapy modalities, number of anti-seizure medications (ASMs), data of seizure diary (types of seizures, frequency, duration) based on caregiver's report in visiting at our hospital or through telephone interviews, VNS parameters, and adverse events were collected. The study protocol was approved by the institutional ethics board at Severance Children's Hospital (IRB No. 4-2020-0120), and informed consent from the patients' parents was obtained.

2.2. VNS implantation and settings

VNS implantation was performed according to standard practice and under general anesthesia. The VNS generator was usually implanted in the left chest (Giordano et al., 2017), which underwent individualized programming by pediatric neurologists. The generator provides intermittent stimulation with set parameters, including the output current, frequency, pulse width, and stimulation on/off times (duty cycle). All the parameters were adjusted to yield the maximum tolerable output current. Our institution's standard settings were as follows: stimulation frequency, 30 Hz; pulse width, 500 ms; signal on time, 30 s; signal off time, 5 min; and output current, 1.5 mA. The magnetic settings were as follows: current, 1.75 mA; on time, 60 s; and pulse width, 500 ms. None of the patients underwent generator reimplantation because of battery service ending.

2.3. Efficacy analyses

Efficacy analysis was performed using an intention-to-treat (ITT) population, which included all eligible patients, using the last observation carried forward (LOCF) imputation method. The monthly mean seizure frequency over three months before VNS implantation was defined as the "baseline." Regular follow-up data regarding the monthly mean seizure frequencies over interval periods at 3, 6, 12, 18, 24, 30, and 36 months after VNS implantation were obtained. Efficacy at each follow-up was measured as the percent reduction in seizure frequency compared to that at baseline. Response was classified as seizure-free, reduction ≥75 %, reduction <75 % to ≥50 %, reduction <50 %, and no change or exacerbation. Responsiveness to VNS therapy was considered as ≥50 % reduction in seizure frequency. Safety was monitored, and adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Magnetic benefit and seizure severity were evaluated based on the available patient records and information collected through telephone interviews.

2.4. Statistical analyses

Data of non-normally distributed continuous variables were presented as medians with interquartile ranges. Chi-square tests were used to analyze categorical data. The Wilcoxon signed-rank method was used to compare seizure frequency between the baseline and follow-up. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS Statistics, version 24 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patient characteristics

Table 1 presents the patient demographics and characteristics at baseline. We included 22 patients (11 males, 50.0 %). The median follow-up duration after VNS implantation was 4.3 years (interquartile range [IQR], 3.0–6.5). All patients had available medical records, including follow-up data for ≥24 months after VNS. Moreover, 19 of the 22 (86.4 %) patients had a follow-up for ≥36 months. Genetic analysis revealed that 20 (90.9 %) patients had pathogenic *SCN1A* mutation. The median age at epilepsy onset was 6.0 months (IQR, 4–8). The predominant seizure type was generalized tonic-clonic seizures in 17 (77.3 %) patients. Before VNS, 17 (77.3 %) patients underwent a ketogenic diet, and two (9.1 %) patients had corpus callosotomy as an epileptic surgery. Median patient age at VNS implantation was 10.0 years (IQR, 7.7–13.3). The median epilepsy duration before VNS therapy was 9.6 years (IQR, 7.3–12.7).

3.2. Efficacy outcomes related to VNS therapy

More than 50 % reduction in seizures was observed in 8 (36.4 %) of the 22 patients at 12 months, 12 (54.5 %) of the 22 patients at 24 months, and 12 (63.2 %) of the 19 patients at 36 months (Fig. 1). Fig. 2

Table 1
Patient characteristics ($n = 22$).

Characteristics	Total
Male, *n* (%)	11.0 (50.0 %)
Follow-up period (months)	52 (35.4–78.4)
Age at epilepsy onset (months)	6.0 (4.0–8.0)
SCN1A gene mutation, *n* (%)	20 (90.9 %)
Age at VNS implantation (years)	10.0 (7.7–13.3)
Epilepsy period before VNS (months)	115.2 (87.3–152.1)
MRI	
Normal	17 (77.3)
Atrophy	4 (18.2 %)
Encephalomalacia	1 (4.5 %)
KD before VNS*	17 (77.3 %)
Brain surgery before VNS	3 (13.6 %)
Corpus callosotomy	2 (9.1 %)
Ventriculoperitoneal shunt	1 (4.5 %)
Number of ASMs in VNS**	4.0 (3.0–5.0)
Number of ASMs***	7.0 (5.5–8.0)

Data are expressed as number (percent) or median (interquartile range).
ASMs, anti-seizure medications; KD, ketogenic diet; MRI, magnetic resonance imaging; VNS, vagus nerve stimulation.
* History of following a ketogenic diet before VNS implantation.
** Number of anti-seizure medications at the time of VNS implantation.
*** Total number of anti-seizure medications tried before VNS implantation.

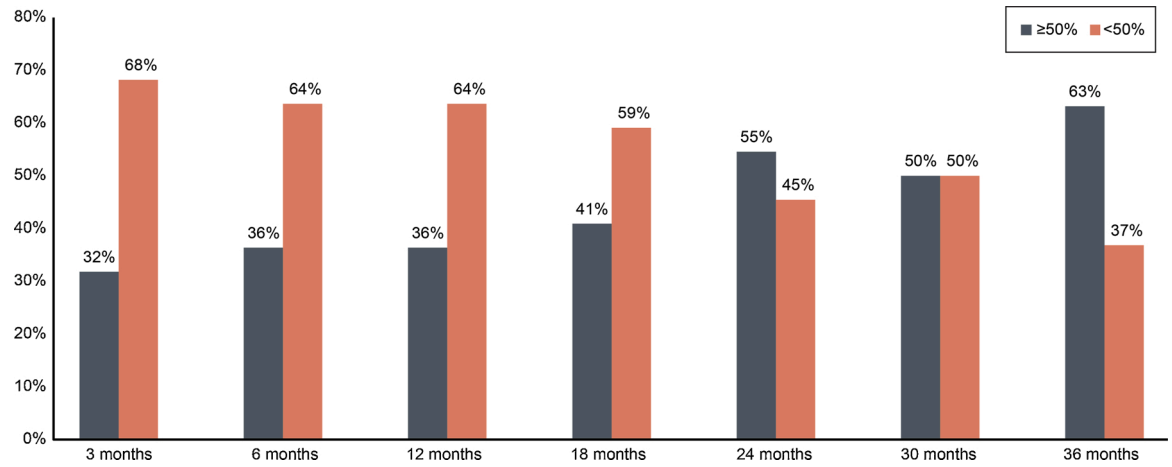

Fig. 1. Seizure reduction outcomes after vagus nerve stimulation (VNS) implantation. More than 50 % reduction in seizure frequency was considered responsive to VNS therapy.

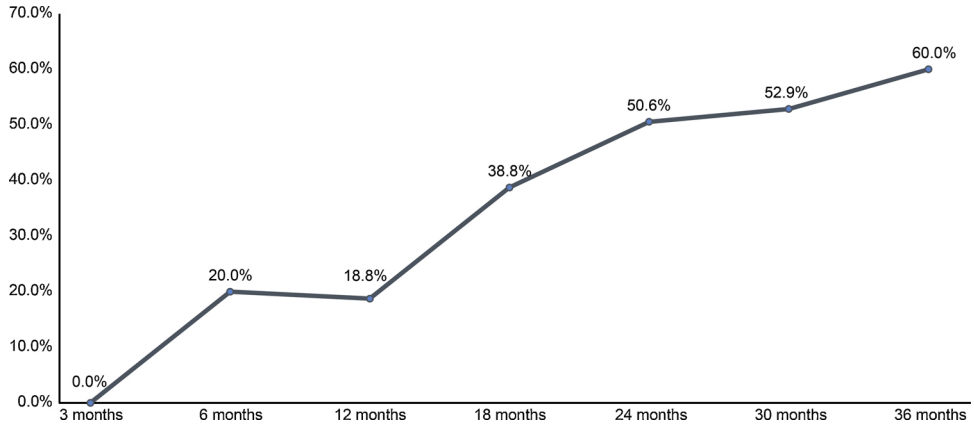

Fig. 2. Median percent reduction in seizure frequency across time after vagus nerve stimulation (VNS) implantation. The median percent reduction in seizure frequency was 18.8 % at the initial 12 months of VNS and was further increased at follow-up.

presents the temporal pattern for the median percent reduction in seizure frequency. The median reduction in seizure frequency was 18.8 %, 50.6 %, and 60.0 % at 12, 24, and 36 months, respectively. The VNS effects on seizure reduction showed a time-dependent progressive increase. Seizure freedom for more than one year was observed in 3 (13.6 %) patients until the last follow-up period. Among them, one patient achieved seizure freedom after 30 months of VNS implantation.

Relative to the baseline values, the seizure frequency was significantly lower at 24, 30, and 36 months, as well as in the longest follow-up period ($p < 0.05$, Wilcoxon signed-rank test) (Table 2).

In addition, throughout the follow-up period, we investigated when the efficacy of VNS began in 12 patients, with ≥50 % reduction in seizures. Eight (8/12, 66.7 %) patients experienced efficacy within the initial 12 months of VNS therapy. However, 4 (4/12, 33.3 %) patients experienced efficacy after 24 months of VNS therapy. Particularly, two patients experienced efficacy at 24 months—one at 30 months and the other at 36 months.

We did not exclude patients who changed ASM during the follow-up period after VNS implantation. Of the patients who had ≥ 50 % reduction in seizures, five patients had reduced the number of ASMs. In 4 patients who had no response to VNS, ASMs had been added (n = 2) or changed (n = 2) during VNS therapy. However, their seizure frequency was not changed, and it did not affect the efficacy of VNS. No patient had undergone epileptic surgery or diet therapy after VNS implantation.

Magnetic effects occurred in 6 (27.3 %) patients from only swiping over a generator at the onset of the seizures or aura (Table 3). However, upon motor seizure onset, swiping a magnet over a generator could not stop seizure activities. Four (18.2 %) patients avoided exposure to magnetic appliances because they had frequent short-duration seizures. The parents of the patients with short-duration seizures did not consider magnets to be useful. The duration per seizure was reduced in 8 (36.4 %)

Table 2
Comparison of seizure frequency between baseline and each period after VNS ($n = 22$).

Variable	*p*-value
3 m*–base**	0.53
6 m*–base**	0.07
12 m*–base**	0.18
18 m*–base**	0.15
24 m*–base**	0.02
30 m*–base**	0.01
36 m*–base**	0.04
Longest*–base**	0.02

Wilcoxon signed-rank tests were used to compare seizure frequency between the baseline and each follow-up visit.
VNS, vagus nerve stimulation.
* Mean seizure frequency over interval periods (per month) at each follow-up after VNS.
** Mean seizure frequency over 3 months (per month) before VNS implantation.

Table 3
VNS-related characteristics ($n = 22$).

Characteristics	Total
Total charges per day (mC)	180 (range 120.0–306.0)
Change in setting*	6 (27.3 %)
Adverse effects	7 (31.8 %)
Hoarseness	4 (18.2 %)
Effectiveness of magnetic	6 (27.3 %)
Effectiveness on duration	8 (36.4 %)
Effectiveness on ictal intensity	11 (50.0 %)
Cognitive effects	12 (54.5 %),
Effectiveness of EEG	10 (45.5 %)

Data are expressed as number (percent) or median (interquartile range).
EEG, electroencephalogram; mC, millicoulomb; VNS, vagus nerve stimulation.
* Change in the standard setting of VNS in our clinics during the follow-up period.

patients. Ictal intensity was improved in 11 (50.0 %) patients. The improvement of duration per seizure and ictal intensity was not always consistent with the reduction in the seizure frequency. The parents of 12 (54.5 %) patients reported a subjective improvement in cognition, communication skills, and general condition after VNS therapy. Most of these patients also had ≥50 % reduction in seizures. However, 2 (16.7 %) of these 12 patients did not show ≥50 % reduction in seizures.

3.3. VNS device parameter response and adverse events

All the VNS parameters were adjusted to yield the maximum tolerable output current. Physicians were allowed to titrate the device settings over the course of the follow-up period. Patients experiencing the efficacy within the initial 12 months significantly had a shorter period to reach their maximum settings than patients experiencing the efficacy after 12 months [median 3.1 months (IQR, 2.9–3.4), median 3.4 months (IQR, 3.2–8.0), p = 0.038, respectively]. However, the VNS standard settings remained the same after 12 months in all patients who had a delayed response. The standard settings used in our center were maintained in 16 (72.7 %) patients. In 6 (27.3 %) patients, the routine settings were changed due to ineffective outcomes or adverse effects (Table 3). The most altered parameters were output current and off time. We changed the VNS setting parameters, with increasing current in one patient, decreasing current in two patients, and changing signal-off time from 5 min to 3 min in three patients. Among them, two patients showed post-modification advantages. Particularly, one patient showed ≥50 % seizure reduction with an increase in current. Another patient experienced adverse events such as hoarseness, deep breathing, and coughing, all of which resolved after reducing the standard current. Adverse events in most patients were less than grade 2 CTCAE version 5.0. The most common symptom associated with adverse events was hoarseness (18.2 %); however, they had temporary or minimal effects on activities of daily living.

4. Discussion

The association between effect of seizure reduction and time after VNS remains unclear in patients with pharmaco-resistant DS. In our study, the median percent reduction in seizure frequency was 18.8 %, 50.6 %, and 60.0 % at 12, 24, and 36 months, respectively. Four (18.2 %) patients who did not experience a decrease in seizure frequency during the first 24 months of VNS therapy eventually benefited from VNS therapy over time. Among them, one patient achieved seizure freedom after 30 months of VNS implantation. Further, there was a significant reduction in seizure frequency from 24 months after VNS therapy. Thus, our results demonstrate that the efficacy of VNS tended to increase over time, which suggests a progressive, time-dependent improvement.

Long-term studies on heterogeneous drug-resistant epilepsy have reported a VNS-induced seizure reduction of ≥50 % in approximately 60 % of the study patients (Elliott et al., 2011). More than 50 % reduction of seizures has been reported in 25–55 % of patients with DS (Dibué-Adjei et al., 2017; Orosz et al., 2014; Zamponi et al., 2011), which was marginally lower than those in the entire population who received VNS (Orosz et al., 2014; Zamponi et al., 2011). Few studies have reported VNS-induced seizure freedom in patients with DS (Dibué-Adjei et al., 2017). In our study, ≥50 % reduction in seizure frequency was observed in 36.4 % (8/22), 54.5 % (12/22), and 63.2 % (12/19) of the patients at 12, 24, and 36 months after VNS therapy, respectively. Seizure freedom for ≥1 year was achieved by 13.6 % of patients. Therefore, our findings indicate that VNS is worthy as an adjunctive treatment for patients with pharmaco-resistant DS over a long-term follow-up period.

Patients can swipe a handheld magnet over the generator when the epileptic aura begins. This triggers stimulus release, which is superimposed with the generator's baseline discharge. This may prevent secondary generalization or terminate the seizure (Zamponi et al., 2011). However, the magnetic efficacy of interrupting prolonged seizures in DS remains unclear (Wirrell et al., 2017). In our study, 27.3 % of parents replied that the swiping magnet was effective at the beginning of seizures or epileptic aura. However, the magnet was ineffective upon motor seizure onset. Because DS patients with intellectual disabilities could not often complain about their aura or detect seizure onset, a magnet might not be considered as helpful by the parents of patients with DS. Evidence for the efficacy of VNS by seizure and epilepsy classification is limited. In one previous study, focal epilepsy or temporal lobe epilepsy predicted improved seizure control compared with other types (Elliott et al., 2011). Orosz et al. reported that patients with predominantly generalized tonic-clonic seizures showed an improvement that was marginally lower than that in the entire population (Orosz, et al., 2014). In our study, there was no significant difference between the generalized tonic-clonic seizures and the other seizure types (data not shown). However, no confident conclusion can be drawn as for seizure types (Zamponi, et al., 2011). Seizure types predicting improved seizure control by VNS therapy remain inconclusive, especially for patients with DS.

Because VNS does not have neurocognitive adverse effects and drug interactions, it is an attractive treatment option for children with DS presenting comorbidities (Fulton et al., 2017; Rossignol et al., 2009). The most common complications of VNS implantation include cough, hoarseness, and breath shortness (Ali et al., 2017; Englot et al., 2011; Rossignol et al., 2009). In our study, 31.8 % of the patients presented adverse effects, with the most frequent being hoarseness. The reported prevalence was consistent with that in the previous findings on other epileptic syndromes and DS. Because most symptoms related to the adverse events had temporary or minimal effects on basic lives, VNS is a safe treatment alternative for DS.

This study has several limitations. First, this study has a small sample size due to the nature of DS, a rare disease. Second, this is not the controlled prospective study that allows the inclusion of a controlled group. In addition, changes in ASMs or VNS setting parameters could be contributing factors to explain the beneficial effects in this study. Therefore, we described in detail changes in ASMs or VNS setting parameters. Moreover, this study may have bias, as it has a single-institution design. Therefore, it is difficult to compare our study results with those of other reports.

5. Conclusions

Our findings, obtained after a long-term follow-up period, suggest that VNS is a safe and suitable adjunctive treatment for pharmaco-resistant DS. Additionally, the seizure reduction effects may gradually improve or appear belatedly over time after VNS implantation. Therefore, longer periods could yield better overall results.

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Declaration of Competing Interest

The authors report no declarations of interest.

References

Ali, R., Elsayed, M., Kaur, M., Air, E., Mahmood, N., Constantinou, J., Schwalb, J., 2017. Use of social media to assess the effectiveness of vagal nerve stimulation in Dravet syndrome: a caregiver's perspective. J. Neurol. Sci. 375, 146–149. https://doi.org/10.1016/j.jns.2017.01.057.

Chiron, C., Marchand, M.C., Tran, A., Rey, E., d'Athis, P., Vincent, J., Dulac, O., Pons, G., STICLO Study Group, 2000. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. Lancet 356, 1638–1642. https://doi.org/10.1016/s0140-6736(00)03157-3.

Devinsky, O., Cross, J.H., Laux, L., Marsh, E., Miller, I., Nabbout, R., Scheffer, I.E., Thiele, E.A., Wright, S., Cannabidiol in Dravet Syndrome Study Group, 2017. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N. Engl. J. Med. 376, 2011–2020. https://doi.org/10.1056/NEJMoa1611618.

Dibué-Adjei, M., Fischer, I., Steiger, H.J., Kamp, M.A., 2017. Efficacy of adjunctive vagus nerve stimulation in patients with Dravet syndrome: a meta-analysis of 68 patients. Seizure 50, 147–152. https://doi.org/10.1016/j.seizure.2017.06.007.

Elliott, R.E., Morsi, A., Kalhorn, S.P., Marcus, J., Sellin, J., Kang, M., Silverberg, A., Rivera, E., Geller, E., Carlson, C., Devinsky, O., Doyle, W.K., 2011. Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. Epilepsy Behav. 20, 57–63. https://doi.org/10.1016/j.yebeh.2010.10.017.

Englot, D.J., Chang, E.F., Auguste, K.I., 2011. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. J. Neurosurg. 115, 1248–1255. https://doi.org/10.3171/2011.7.Jns11977.

Fulton, S.P., Van Poppel, K., McGregor, A.L., Mudigoudar, B., Wheless, J.W., 2017. Vagus nerve stimulation in intractable epilepsy associated with SCN1A gene abnormalities. J. Child Neurol. 32, 494–498. https://doi.org/10.1177/0883073816687221.

Giordano, F., Zicca, A., Barba, C., Guerrini, R., Genitori, L., 2017. Vagus nerve stimulation: surgical technique of implantation and revision and related morbidity. Epilepsia 58 (Suppl 1), 85–90. https://doi.org/10.1111/epi.13678.

Harkin, L.A., McMahon, J.M., Iona, X., Dibbens, L., Pelekanos, J.T., Zuberi, S.M., Sadleir, L.G., Andermann, E., Gill, D., Farrell, K., Connolly, M., Stanley, T., Harbord, M., Andermann, F., Wang, J., Batish, S.D., Jones, J.G., Seltzer, W.K., Gardner, A., Sutherland, G., Berkovic, S.F., Mulley, J.C., Scheffer, I.E., 2007. The spectrum of SCN1A-related infantile epileptic encephalopathies. Brain 130, 843–852. https://doi.org/10.1093/brain/awm002.

Kossoff, E.H., Zupec-Kania, B.A., Auvin, S., Ballaban-Gil, K.R., Christina Bergqvist, A.G., Blackford, R., Buchhalter, J.R., Caraballo, R.H., Cross, J.H., Dahlin, M.G., Donner, E. J., Guzel, O., Jehle, R.S., Klepper, J., Kang, H.C., Lambrechts, D.A., Liu, Y.M.C., Nathan, J.K., Nordli Jr., D.R., Pfeifer, H.H., Rho, J.M., Scheffer, I.E., Sharma, S., Stafstrom, C.E., Thiele, E.A., Turner, Z., Vaccarezza, M.M., van der Louw, E., Veggiotti, P., Wheless, J.W., Wirrell, E.C., Charlie Foundation, Matthew's Friends, Practice Committee of the Child Neurology Society, 2018. Optimal clinical management of children receiving dietary therapies for epilepsy: updated recommendations of the International Ketogenic Diet Study Group. Epilepsia Open 3, 175–192. https://doi.org/10.1002/epi4.12225.

Lagae, L., Sullivan, J., Knupp, K., Laux, L., Polster, T., Nikanorova, M., Devinsky, O., Cross, J.H., Guerrini, R., Talwar, D., Miller, I., Farfel, G., Galer, B.S., Gammaitoni, A., Mistry, A., Morrison, G., Lock, M., Agarwal, A., Lai, W.W., Ceulemans, B., FAiRE DS Study Group, 2019. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet 394, 2243–2254. https://doi.org/10.1016/s0140-6736(19)32500-0.

Liu, Y., Lopez-Santiago, L.F., Yuan, Y., Jones, J.M., Zhang, H., O'Malley, H.A., Patino, G. A., O'Brien, J.E., Rusconi, R., Gupta, A., Thompson, R.C., Natowicz, M.R., Meisler, M.H., Isom, L.L., Parent, J.M., 2013. Dravet syndrome patient-derived neurons suggest a novel epilepsy mechanism. Ann. Neurol. 74, 128–139. https://doi.org/10.1002/ana.23897.

Orosz, I., McCormick, D., Zamponi, N., Varadkar, S., Feucht, M., Parain, D., Griens, R., Vallée, L., Boon, P., Rittey, C., Jayewardene, A.K., Bunker, M., Arzimanoglou, A., Lagae, L., 2014. Vagus nerve stimulation for drug-resistant epilepsy: a European long-term study up to 24 months in 347 children. Epilepsia 55, 1576–1584. https://doi.org/10.1111/epi.12762.

Rossignol, E., Lortie, A., Thomas, T., Bouthiller, A., Scavarda, D., Mercier, C., Carmant, L., 2009. Vagus nerve stimulation in pediatric epileptic syndromes. Seizure 18, 34–37. https://doi.org/10.1016/j.seizure.2008.06.010.

Scheffer, I.E., Berkovic, S., Capovilla, G., Connolly, M.B., French, J., Guilhoto, L., Hirsch, E., Jain, S., Mathern, G.W., Moshé, S.L., Nordli, D.R., Perucca, E., Tomson, T., Wiebe, S., Zhang, Y.H., Zuberi, S.M., 2017. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 58, 512–521. https://doi.org/10.1111/epi.13709.

Wirrell, E.C., Laux, L., Donner, E., Jette, N., Knupp, K., Meskis, M.A., Miller, I., Sullivan, J., Welborn, M., Berg, A.T., 2017. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a North American consensus panel. Pediatr. Neurol. 68, 18–34. https://doi.org/10.1016/j.pediatrneurol.2017.01.025 e3.

Wu, Y.W., Sullivan, J., McDaniel, S.S., Meisler, M.H., Walsh, E.M., Li, S.X., Kuzniewicz, M.W., 2015. Incidence of Dravet syndrome in a US population. Pediatrics 136, e1310–e1315. https://doi.org/10.1542/peds.2015-1807.

Zamponi, N., Passamonti, C., Cappanera, S., Petrelli, C., 2011. Clinical course of young patients with Dravet syndrome after vagal nerve stimulation. Eur. J. Paediatr. Neurol. 15, 8–14. https://doi.org/10.1016/j.ejpn.2010.09.003.