We present a case study of vagus nerve stimulation to treat epilepsy in an adult male with fragile X syndrome. This patient had seizures beginning at about two years of age. He did relatively well on anticonvulsant medications until reaching his thirties, when he experienced a resurgence of seizures, occurring about twice per week, and a decline in overall functioning. During one year of vagus nerve stimulation, he had a total of four to five seizures, his adaptive behavior and socialization improved, and he had reduced irritability and aggression. The possible benefits of vagus nerve stimulation in relation to what is known about brain morphology and function in fragile X is explored.

Keywords: aggression, autism, developmental, epilepsy, FMR1 gene, fragile X syndrome, intellectual disability, mental retardation, mood, psychiatric, seizures, stimulation, vagus nerve stimulation

Genotype and Phenotype of Fragile X Syndrome

Fragile X syndrome (FXS), caused by a mutation in a single gene on the long arm of the X chromosome, occurs in 1 of every 2,000 to 5,000 live births and is the most common known inherited cause of developmental disability. The cytogenetic fragile site on the X chromosome from which the syndrome derives its name is typically caused by the presence of more than 200 cytosine-guanine-guanine (CGG) triplet repeats within the promoter region of the fragile X mental retardation (FMR1) gene. The presence of > 200 repeats is termed a full mutation and is associated with methylation, which decreases or prevents normal transcription. The transcriptional silencing of the gene and the resultant diminished or absent production of the FMR1 protein (FMRP) results in aberrant brain development and the phenotypic features of the syndrome.16,50 Males with FXS typically exhibit characteristic physical features such as prominent ears, a long narrow face, hyper-extensible finger joints, flat feet, and macroorchidism.24 There is also a prominent behavioral phenotype that includes hyperarousal, social anxiety and withdrawal, gaze aversion, attention problems, unusual responses to sensory stimuli, stereotypic behavior, and impulsivity.5-7,10-13,21,25,37,42 Autism occurs in approximately 15% to 33% of individuals with FXS.4,44,45

Seizures in Fragile X Syndrome

Seizures are found to be the most common neurological abnormality in individuals with FXS,24 (p. 112) with an estimated prevalence of 23%, based on a review of 285 individuals.39 Most children with FXS outgrow their seizures; however, about one-quarter of those with epilepsy continue to have seizures into adulthood. Most individuals are well controlled on anticonvulsant medications; however, an occasional individual has epilepsy that is very difficult to control with pharmacological treatment.

The cause of seizures in FXS is not known; however, recent neuroanatomical and electrophysiological studies have provided important clues. One such clue comes from studies of fragile X knockout mice. These mice have been genetically altered to knockout, or prevent any function of the FMR1 gene. Musumeci and colleagues40 showed that these mice have increased susceptibility to audiogenic seizures as compared to wild-type littermates. Studies of FMR1 knockout mice and post-mortem brain tissue of FXS individuals show abnormal density and morphology of dendritic spines,29,30 perhaps as a result of delayed maturation and
deficiency of normal neuronal pruning. These structural abnormalities may be associated with excessive neuronal excitation, resulting in increased susceptibility to seizure activity. Rojas reported that individuals with FXS responded to auditory stimuli with increased magnetoencephalography field strength, a measure that is directly proportional to the number of synchronously active cells in the cortex. Ferri and colleagues found hyper-excitability in the supplementary motor area in a small sample of males with FXS, and in one individual finger tapping induced the appearance of left parietal-evoked EEG spikes. Altered GABA, increased glutamate release, decreased adenosine and effects of other opiate peptides also may be involved in increasing susceptibility to seizures. For example, studies in the laboratory of Ted Brown have shown a lack of normal GABA inhibition that can lead to hyperactivity and seizures. In summary, we believe that the underlying factors listed above predispose individuals with FXS to seizures.

Vagus Nerve Stimulation

Nerve fibers in the vagus nerve that carry information from the body’s organs to the brain are believed to be involved in producing seizures. Stimulation of the vagus nerve has been suggested to disrupt epileptic activity with research demonstrating that vagus nerve stimulation (VNS) therapy aids in the treatment of seizure disorders. The VNS works by alternating between repeatedly stimulating the vagus nerve for a discrete period of time with periods of pausing. According to Le and colleagues, VNS has been shown to reduce partial and generalized seizure activity by approximately 50%. A large double blind study of VNS treatment in 114 individuals demonstrated a 45% reduction of seizures at 12 months. Thirty-five percent of 195 individuals had a greater than 50% reduction of seizures and 20% had a greater than 75% reduction in seizures during the one year period. In addition, a series of studies also have demonstrated its efficacy in reducing seizure activity and improving quality of life in Lennox Gastaut syndrome, a disorder characterized by medication-resistant seizures in childhood. The details of how seizure frequency is reduced with VNS remains unknown, though some argue that it aids in desynchronization of brain activity which may decrease seizure activity.

Case Study

The following is a case study of the use of VNS to control epilepsy in an individual with FXS and documentation of the benefits of this novel intervention for individuals with this syndrome.

Mr. N is 34-year-old Hispanic male diagnosed with FXS at age 15. The pregnancy and delivery of this case was unremarkable. He had a right ear deformity that reportedly resolved by one year of age. His early history was notable for general developmental delay, perseverative and obsessive-compulsive behaviors, hand flapping, poor eye contact, tactile defensiveness and hyperactivity. He had significant social difficulties that led to a diagnosis of autistic disorder at age four. His first recognized seizure also occurred at four years of age. This was a grand mal seizure that led to status epilepticus that lasted at least one hour. He subsequently had intermittent status epilepticus once or twice a month, often resulting in hospitalization. He was initially tried on phenobarbital, but he became much more hyperactive. He was then started on phenytoin that was used for a number of years. In adolescence he was switched to carbamazepine and his seizures changed to a cluster type with 8-12 seizures per day that seemed to begin as a partial motor seizure and then evolved into partial complex seizures, often with auras, fearful behavior, and reaching for a caregiver prior to the seizure. His family members have noted that many, though not all of his seizures have occurred during or following overstimulating activities such as social events. Indeed, Mr. N had elements of several seizure types, including characteristics of reflex epilepsy and status epilepticus, and motor behavior prior to change in level of consciousness.

He has taken a variety of medications since childhood, including tiagabine and gabapentin for seizure management, risperidone for aggression and mood instability, clonazepam for anxiety, and medications for constipation. Fluoxetine was also started at age 29, after the death of his father, to treat symptoms of anxiety and depression. His medications were used in quite high dosage and he had been on as many as five medications at one time.

The decision to implant a VNS was made by his neurologist due to poor seizure control and unacceptable medication side effects. The implantation occurred in September 2001. His neurological status, overall cognitive functioning, adaptive and maladaptive behavior, and receptive
language were evaluated before and after one year of VNS treatment.

On his first visit, prior to VNS treatment, Mr. N was unable to separate from his mother and did not give eye contact, burying his head in her arms for the majority of the examination. Although not motivated to participate in the evaluations, Mr. N tolerated questions by pointing to answers or giving one or two word responses. He was able to engage in simple conversation, but had mild echolalia, as well as repetitive and tangential speech. On the second visit, one year after initiating VNS treatment, he appeared to be less anxious and he was able to separate from his mother. His family also indicated that Mr. N often showed extremely fearful behavior at bedtime and reported seeing monsters in his bedroom. Regarding change in seizure frequency, he had approximately one to two seizures per week prior to VNS placement in comparison to two seizures during the first 5 months of his VNS treatment.

The Autism Diagnostic Interview - Revised \(^{34}\) was conducted with his mother during the first visit, prior to VNS treatment. In terms of his early childhood behavior (ages 4-5), he was just over the threshold for autism in two of the three areas evaluated (communication and repetitive behavior and interests). On the Autism Diagnostic Observation System - Generic \(^{32}\) he did not meet criteria for autism in two of the three domains - social interaction and communication. According to these measures, Mr. N presented with many behavioral features of autism, but did not meet full diagnostic criteria, and thus was characterized as having Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS). He also met DSM-IV diagnostic criteria for Social Phobia based on clinical observation and family interview.

The Vineland Adaptive Behavior Scales: Interview Edition \(^{48}\) was administered to Mr. N's mother before and after one year of VNS treatment. While his communication skills appeared largely unchanged, according to his family, he made moderate gains in daily living and socialization skills. During the interview, his mother and sister described that his attention and organization for daily living tasks and his openness for socialization improved considerably. Prior to VNS treatment he was very dependent on others for self-care and hygiene, had difficulty expressing thoughts and feelings, and was quite withdrawn and resistant to giving and receiving affection. At the second interview, after one year of VNS treatment, family members reported increased independence with self-care, improved quality and quantity of communication, and much more interest in relating to others socially. His mother completed the Aberrant Behavior Checklist - Community version \(^{3}\) as measures of problem behavior prior to and during treatment. According to her report, Mr. N had significant decreases in irritability, lethargy, and hyperactivity. Prior to treatment, he was aggressive, had frequent temper tantrums or outbursts, and experienced pronounced mood changes (see Table 1 for scores). During treatment with VNS, no symptoms of irritability were reported, and he was described as more social and less hyperactive. Despite these improvements, he had some worsening of anxiety symptoms. He had two panic attacks during the year of VNS treatment, one occurring during adjustment of his stimulator and one during a camping trip. The family indicated that the former may have been triggered by the actual adjustment of the device, and they reported that the latter occurred when he thought he was going to have a seizure. An occasional increase in fearful behavior was also noted before going to bed.

Cognitive ability, as measured by the Wechsler Abbreviated Scale of Intelligence (WASI), \(^{51}\) and receptive language, as assessed by the Peabody Picture Vocabulary Test - Third Edition (PPVT-III) \(^{18}\) showed no change before and after VNS treatment; however, it should be noted that Mr. N scored at or near the floor on these measures (IQEst = 55; PPVT-III = 40). Dodrill and Morris \(^{17}\) also reported similar findings in examination of cognitive functioning post VNS treatment.

Following two years of VNS, Mr. N continued to have significant response to the therapy. His seizure frequency was 4-5 seizures in the past year, and he has had a reduction in number and total dosages of his medications.

**Discussion**

We have reported here the neurological, adaptive, and behavioral benefits of VNS in an individual with FXS and epilepsy, as well as
TABLE 1. SUMMARY OF VINELAND ADAPTIVE BEHAVIOR AND ABERRANT BEHAVIOR CHECKLIST
STANDARD SCORES WITHIN EACH DOMAIN FOR EACH EVALUATION PERIOD

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<td>31</td>
<td>Inappropriate Speech</td>
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Aberrant Behavior Checklist3; Vineland Adaptive Behavior Scales48

several comorbid features including PDD-NOS and Social Phobia. Mr. N’s seizure frequency was significantly reduced by the treatment, which may have contributed to positive behavioral and psychiatric changes observed. Reduction of mood-related symptoms such as disposition and dysphoria associated with VNS treatment have been previously reported in the literature.26,43 and increases in quality-of-life have been documented.14,19,23,26,43 The VNS was well tolerated, and no significant adverse effects were reported. Although Mr. N was currently taking medications for a variety of symptoms, it is important to note that changes in medications or dosages did not occur just before or during the course of his VNS treatment.

VNS may be especially effective for individuals with FXS. Recent studies have documented that individuals with FXS have increased sympathetic nervous system reactivity to several types of sensory stimuli,38 low levels of vagal tone, and poor modulation of vagal tone in response to changing task demands.43 Vagal tone is thought to be involved in the autonomic system’s role in emotion regulation. Thus, VNS may not only help to reduce seizure activity, but may also enhance vagal tone that is otherwise reduced in FXS.

Decreased irritability and increased socialization observed in our patient may be associated with positive physiological effects. This interpretation is supported by a recent 60-person study of VNS for treatment-resistant depression.46 In this study, 40% of individuals who had failed an average of 4.8 previous treatments had at least 50% improvement in the Hamilton Rating Scale for Depression scores and 21% achieved complete remission after three months of VNS treatment. The possible effectiveness of VNS in treating anxiety disorders has also been described by Schachter,47 who posits that information carried by the vagus nerve is an important part of anxiety regulation. He also noted that reductions in anxiety were quite robust among the depressed individuals described above.

While brain mechanisms underlying these mood and behavioral changes are not clear, recent brain imaging studies in individuals with epilepsy have shown that acute VNS affects limbic and paralimbic regions known to modulate mood, including the orbitofrontal cortex, hypothalamus, and amygdala, along with increased mood effects and changes in brain monoamine.47 However, it should be noted that improvements in quality of life and mood may not necessarily be directly due to VNS. For example, reduction of anticonvulsi medication may be helpful to reduce arousal and irritability.

Given our patient’s mixture of seizure and anxiety symptoms, it is important to note that some of the factors attributed to seizures are also noted in panic and other anxiety disorders. In some cases, it is difficult to differentiate complex partial seizures from a range of anxiety-related symptoms, and anxiety disorders are common for many individuals referred with intractable epilepsy. For example, fear, depersonalization/derealization, dissociation, and déjà vu are often reported. Interestingly, relatives of our patient noted that his seizures occurred following stressful or highly arousing events.

There were a number of factors that may be attributable to this individual’s clinical
improvement other than his vagus nerve treatment. First, his family moved shortly after the initiation of his treatment. According to reports from the family, Mr. N has benefitted from better care and an improved living situation, which may have resulted in a positive change in functioning. Second, because family members reported retrospectively on his clinical status, they may have been susceptible to positive response bias. Third, improved alertness from the VNS may also have contributed to behavioral improvement. Fourth, while we feel it is unlikely, a placebo effect resulting in real behavioral changes not directly a result of the VNS could have occurred. Finally, maturational changes or natural variation in symptomatology may have been associated with his improvement. Future studies examining VNS in a larger group of individuals with FXS may confirm its effectiveness in treating epilepsy, and perhaps mood instability and anxiety that are hallmark psychiatric features of this condition.

REFERENCES


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