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Case Report

Noninvasive treatment alternative for intractable startle epilepsy

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ABSTRACT

We describe a treatment alternative for intractable, startle-provoked, epileptic seizures in four children aged between 8 and 14. Three of the four children had symptomatic localization-related epilepsy. They all suffered from intractable epilepsy precipitated by sudden sounds. The fact that seizures tended to occur with high frequency – more than one seizure a day – had a clear impact on daily life. Clinical seizure pattern demonstrated asymmetric tonic posturing in all four children. Three children experienced several seizure types including focal seizure onset. All children had focal neurological signs or learning disabilities or a combination of both. Our noninvasive treatment method using psychoeducational counseling and sound generators was applied in four children, resulting in a seizure frequency reduction of ≥50% in two of them.

1. Introduction

Startle-provoked epileptic seizures (SPES) are not a uniform epileptic entity. The majority of children with SPES are known to have a congenital brain condition or an acquired brain injury which occurred early in life [1–5]. Seizures tend to be highly refractory, and impact on daily life and psychomotor development over time is high. Several authors report a favorable outcome of epilepsy surgery, although numbers are small [2,3,6,7].

Unexpected sounds are the stimuli most frequently found to precipitate SPES, although somatosensory and visual stimuli have also been reported. Background sounds are known to reduce startle responses in a positive way. In the case of a weak prepulse — a soft sound ahead of the startle inducing sound, reduction of startle response and perceived stimulus is reported [8]. In the audiological field, psychobehavioral therapies are regularly used to reduce symptoms caused by an oversensitivity to sounds, for instance, in the conditions tinnitus or hyperacusis. Most treatments are based on the tinnitus-retraining therapy introduced by Jastreboff [9]. The usage of sound generators (tinnitus masker) or hearing aids is part of this therapy. The effect of background sounds on startles and the use of sound generators in psychobehavioral therapy in the audiological field were the bases for a treatment alternative for SPES. In patients with epilepsy, Brown and Fenwick have already described a positive effect of behavioral therapy on seizure activity [10]. We report four children with SPES. One of the boys with SPES reported an improvement in seizure frequency during holidays, especially when staying at the beach, where he heard the sound of waves breaking continuously. This was the basis for considering a treatment alternative for SPES. We combined both methods (relaxation and distraction) and can now report nonpharmaceutical seizure-management in 4 children with intractable SPES predominantly triggered by auditory stimuli. We used a noninvasive method consisting of a combination of psychoeducational counseling and sound generators.

2. Case reports

Four children, all male, aged between 8 and 14, suffered from intractable epilepsy precipitated by sudden sounds.

2.1. Patient 1

Patient 1 is male, firstborn of healthy parents; pregnancy and delivery were uneventful. Neonatal period was complicated by a group B meningococcal sepsis. Seizures occurred from the age of fourteen months,

Abbreviations: SPES, startle-provoked epileptic seizures; ASR, acoustic startle reflex; MR, magnetic resonance.

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and he developed an epileptic encephalopathy. He suffers from myoclonic seizures of the left arm, atonic seizures, and tonic seizures. The latter were provoked by sudden sounds or unexpected visual stimuli. Neurological examination revealed no focal abnormalities; there is a psychomotor developmental delay with severe learning disabilities. Extended diagnostic work-up, including magnetic resonance (MR) imaging and MR spectography, and neurometabolic and genetic evaluation were all normal. Three seizure types have coexisted since the onset of epilepsy. He was not a suitable candidate for epilepsy surgery. At the age of 5 years, a vagal nerve stimulator was implanted, and a revision took place after two years because of dysfunction and increase in seizure frequency. Ketogenic diet had no effect. At age 10, his epilepsy was still refractory, with seizure frequency varying from several seizures a day to 30 seizures a day, depending on triggering factors. He used lamotrigine and clorazepam at the time of referral to the audiological team. Treatment alternative with sound generators was initiated after counseling both the boy and his parents. During a follow-up period of a year at the child neurology outpatient clinic, his parents reported that he continuously removed his retrainers. As there was no change in seizure frequency, they stopped the sound generator therapy.

2.2. Patient 2

Patient 2 is the third son of healthy parents, born after an uneventful pregnancy and delivery. At age three months, he suffered from pneumococcal meningitis. He developed a spastic right-sided hemiplegia and localization-related complex partial seizures over a period of two years. He became seizure-free and did not use antiepileptic drugs for several years until he developed startle seizures at age 10. A sudden sound resulted in a tonic seizure, sometimes accompanied by urinary or fecal incontinence. Seizure frequency was variable, depending on triggering factors such as a pencil falling in the classroom or a school bell ringing. He had at least 2–3 seizures a day; they did not respond to antiepileptic drugs. He attends a normal school. His MR imaging showed an encephalomalacia of the left hemisphere. Epilepsy surgery was considered, but his parents preferred the noninvasive treatment alternative with sound generators. He and his parents were counseled by our audiological team, and therapy with sound generators was initiated with considerable success. Over a period of a few years, seizure frequency was reduced to one per month. He was even able to watch fireworks and to set one off himself when wearing his sound generators.

2.3. Patient 3

Patient 3 was born of healthy parents; pregnancy and delivery were uneventful. He is known to have Von Willebrand's disease. He experienced a traumatic head injury due to a fall from a trampoline at the age of four years and 6 months complicated by intraparenchymal bleeding and subdural hematoma with mass effect requiring evacuation twice. Magnetic resonance imaging reveals a cystic encephalomalacy of the right cerebral hemisphere and postcontusional abnormalities of the left frontal lobe. He has a left-sided hemiparesis, neglect, and hemianopia. He has learning disabilities and a behavioral disorder. He suffers from simple partial seizures with a tingling sensation of the left side of his face and startle-provoked tonic seizures with posturing of left arm and deviation of head and eyes to the left. The startle-provoked seizures increased in frequency from the age of 7 and were refractory. He uses oxcarbazepine and clobazam. During the work-up for epilepsy surgery, treatment alternative with sound generators was tried and proved effective but not curative. His seizure frequency decreased from several seizures a day prior to the sound generator therapy to one seizure a day during the follow-up period of six months at the child neurology outpatient clinic. He subsequently underwent a temporoparietooccipital disconnection in the right hemisphere at age nine.

2.4. Patient 4

Patient 4 is a boy, born at term, of healthy parents; pregnancy was uneventful but delivery was complicated by peripartal asphyxia. He suffers from infantile encephalopathy with learning disabilities, a predominantly left-sided tetraplegia, and localization-related epilepsy. Magnetic resonance imaging reveals ischemic lesions in the right hemisphere and the left frontal lobe. From the age of eight, he has suffered from complex partial seizures of the left part of the body; initially, he responded well to antiepileptic drugs. After two years, the seizures became startle-provoked; unexpected sounds gave rise to increase in seizure frequency and seizure severity. Tonic seizures occurred at least 3 times a day, sometimes in a cluster of more than an hour despite the use of levetiracetam, lamotrigine, and clobazam. He was referred to our audiological team in parallel with the work-up for epilepsy surgery. Treatment alternative with sound generators had no effect on seizure frequency. Functional right-sided hemispherectomy was performed at age fourteen.

In two boys (patients 1 and 2), seizures could also be triggered by unexpected visual stimuli. Seizures tend to occur with high frequency, more than one seizure a day, exerting a considerable impact on daily life and psychomotor development. Clinical seizure pattern involved asymmetric tonic posturing in all four children. Three children demonstrated several seizure types including focal seizure onset. All children had focal neurological signs or learning disabilities or a combination of both. Auditory examination revealed normal auditory functions in all four. (For a more detailed description of case history, see Table 1.)

2.5. Intervention

All four children and their parents were counseled by the same team of audiologists and followed a tailor-made treatment protocol for each child adapted from ‘the specialised care treatment protocol’ of Cima et al. [11]. After a simple, understandable explanation of the auditory system, the purpose of the sound generators was explained.

The sound generator is a Beltone TBR (tinnitus breaker) 62D, non-occluding open fit. This small instrument does not block the external auditory canal. A sound generator produces a preset, broadband, background sound just audible in silence. This background sound does not disturb conversation, nor does it attract the child's attention continuously. The sound generators are fitted in both ears.

The sound produced by the sound generators does not prevent or mask startle-inducing sounds. During several visits, the frequency spectrum of the noise produced by the sound generators is adjusted to create a sound in which the child recognizes a known pleasant sound (e.g., whispering creek or rustling wind through the trees). The intensity of the sound can be heard when it is focussed on in silence, but the aim is for the child to become accustomed to it. The sound generators should create a relaxing mood and offer a feeling of control over the auditory environment.

2.6. Summary

Seizure frequency reduction of 50% or more occurred after appropriate fitting and counseling by the audiologists in two out of four children. One of the nonresponders repeatedly removed the sound generators. Two boys, one of whom experienced no effect at all from the intervention, successfully underwent epilepsy surgery.

3. Discussion

Lesions responsible for SPES are highly diverse including epileptogenic lesions of supplementary motor and sensorimotor areas and primary sensorimotor, premotor, and perisylvian cortices [1–4]. Emotional and psychodynamic factors also play a role in the pathogenesis of SPES. In all four children, seizures were precipitated by an acoustic

Table 1

Case	Patient 1:	Patient 2:	Patient 3:	Patient 4:
Age at epilepsy onset	14 months	3 months	4 years and 6 months	8 years
Age at startle epilepsy onset	14 months	10 years	4 years and 6 months	10 years
Cognitive functioning	Severe learning disabilities	Mild learning disabilities	Learning disabilities and behavioral disorder	Learning disabilities
Neurologic examination	None	Right-sided spastic hemiplegia	Left sided hemiplegia, neglect, and hemianopsia	Left-sided hemiplegia and dysarthria
MRI	Normal	Encephalomalacy of the left hemisphere	Encephalomalacy of the right hemisphere and the left frontal lobe	Ischemic lesions in the right hemisphere and left the frontal lobe
Etiology	Unknown	Pneumococcal meningitis at the age of 3 months	Traumatic intracranial hemorrhage at the age of 4.5 years (Von Willebrand's disease)	Perinatal asphyxia
Seizure frequency	Several seizures/day	Several seizures/day	Several seizures/day	>3 seizures/day
Semiology	Myoclonic seizures of the left arm Tonic seizures triggered by auditory and visual stimuli Atonic seizures	Generalized tonic seizures triggered by unexpected sounds Complex partial seizures with deviation of eyes and sometimes head to the left and extension of the arms	Tingling sensations of the left side of the face Complex partial tonic seizures with deviation of head and eyes to the left and extension of the left arm triggered by unexpected sounds	Tonic seizures consisting of extension of left arm and leg triggered by unexpected sounds
Ictal EEG	Rhythmic saw-tooth discharges in bilateral frontal areas. Diffuse 9-to 10-Hz rhythmic activity followed by decrement	Rhythmic 2-to 3-Hz activity in the right frontotemporoparietal area spreading to the left frontal area and midline. With versation of head and eyes, the rhythmic activity increases in frequency to 10Hz over vertex followed by bilateral synchonized delta activity which extinguishes	Decline of slow activity in the right parietal occipital region	During seizures suppression of background pattern, no localizing start
Interictal EEG	Delayed undifferentiated background pattern, highly frequent multifocal epileptiform discharges	Slight asymmetry in background pattern, no focal or epileptiform discharges	Normal background activity with an asymmetry detrimental to the right hemisphere; right-sided focal epileptic discharges parietal	Delayed background pattern with an asymmetry to the right hemisphere; paroxysmal sharp wave activity with varying maximum in the right hemisphere
AED	LTG, CLB	CBZ	OXC, CLB	CLB, LTG, LEV
Ketogenic diet	+	−	−	−
VNS	+	−	−	−
Epilepsy surgery	−	−	Temporo-parieto-occipital disconnection in the right hemisphere	Functional right-sided hemispherectomy
Auditory examination	Behavioral observation Audiometry[a]: responses to broadband noise as well as warble tones at levels between 30 and 40 dBA; good listening attitude Well aeriated middle ears TEOAE: ADS emissions. ABR: normal morphology at stimulation level of 70 dBHL Conclusion auditory system: sub-normal auditory thresholds; no indications for abnormal responses and potential pathology in the auditory system up to the brainstem	Auditory thresholds[a]: ADS: between 0 and 5 dBHL for all frequencies. Well-aerated middle ears Speech audiometry: SRT ADS: 5 dB. 100% speech discrimination at a level of 65 dB ABR not measured No indications of hyperacusis Conclusion auditory system: Normal auditory thresholds. No indications for abnormal responses and potential pathology in the auditory system up to the brainstem	Auditory thresholds[a]: AD at around 15 dBHL and AS at around 10 dBHL for all frequencies Well-aerated middle ears Speech audiometry: SRT AD: 15 dB; AS 10 dB. 100% speech discrimination at a level of 70 dB ABR: pattern with poor morphology and AS wave V latency delayed. Wave V disappears at around 40dBnHL No indications of hyperacusis Conclusion auditory system: Normal auditory thresholds; ABR indicative for possible retrocochlear auditory dysfunction	Auditory thresholds[a]: ADS between 0 and 5 dBHL for all frequencies Well-aerated middle ears Speech audiometry: SRT ADS: 5 dB. 100% speech discrimination at a level of 65 dB ABR not measured Conclusion auditory system: normal auditory thresholds
Seizure frequency reduction ≥50% since starting the use of retrainers	−[b]	+	+	−

Abbreviations: ADS = auricula dextra et sinistra, AEDs = antiepileptic drugs, ASR = acoustic startle reflex, CBZ = carbamazepine, CLB = clobazam, dBHL = decibels Hearing Level, dBnHL = decibels normal Hearing Level, LEV = levetiracetam, SRT = speech reception threshold, OXC = oxcarbamazepine.

[a] Tympanometry: ADS Type A.

[b] Continuously removal of retrainers.

startle, although it is unclear whether the sound or the physical startle response induced the seizure.

In the acoustic startle reflex (ASR), a sudden sound mechanically activates a signal in the hair cells in the inner ear which is transmitted via the n. VIII. The signal synapses at the nucleus cochlearis, nucleus reticularis pontis caudalis, and various motor neurons which prepare the body to adopt a stable position. This stable position is called the acoustic startle response. Fig. 1a is a schematic representation of the neuronal pathways involved during an emotional response (e.g., a fear response) to an auditory stimulus. Simultaneously with the pathway of the ASR, the sound signal is also transferred along the auditory pathway. The (indirect) subcortical pathway prepares the amygdala for triggering a defensive response; this is not, however, carried out until the stimulus from the (direct) cortical pathway confirms the existence of a threat. The defensive response (fight or flight reaction) consists of activating sensory changes, such as increased auditory attention, and autonomic changes, such as an increase in adrenaline level (Fig. 1a).

In SPES, the ASR itself or the muscular jerk (proprioceptive input of the startle reaction) caused by the initial startle can be the cause of the seizure [2]. The accompanying fear of having a seizure might also be an extra triggering factor. This was already described by Fenwick and Brown who reported several patients provoking seizures by specific movements or thoughts [12]. In some children, seizure frequency increased when they were startled more often or more easily due to fear of a seizure. This feature is also seen in psychiatric disorders associated with a dysfunction of the fear response (e.g., posttraumatic stress disorder, panic attacks, and phobias), and people with these disorders are more easily startled as well. It has been suggested that this abnormal ASR is the result of a hypersensitive amygdala, and Bakker et al. supported this theory [13]. They found a normalization of the ASR after successful behavioral treatment in children with anxiety disorders.

In the neurophysiologic model of tinnitus proposed by Jastreboff et al. [14], the amygdala plays an important role (Fig. 1b) [9]. Because of the involvement of the amygdala in the acoustic startle, we used a form of tinnitus-retraining therapy, adapted from Jastreboff, which consists of a combination of psychoeducational management and sound generators. To our knowledge, this is the first application of sound generators in the treatment of SPES; hence, placebo-controlled trials are needed to confirm efficacy. Possible explanations for the effect of the intervention might be a decrease in sensitivity preventing an ASR from being induced. The continuous sound produced by the sound generators masks sudden onset sounds. But a reassuring effect due to the reduction of fear and aroused state and, moreover, an increase in well-being and the feeling of control the sound generators give may also play an important role. We, therefore, cannot exclude a placebo effect of the sound generators, as children are twice as likely as adults to respond with a greater than 50% reduction in seizure frequency during placebo treatment [15]. In our small population, the sound generators were effective in two out of four children. The responding two children are able to communicate and understand the instructions explaining the usage of the sound generators; this seems to be of importance. We suggest that this noninvasive therapy in refractory SPES be considered early on in the treatment strategy of SPES, as there is no downside to the trial with the intervention of psychoeducational counseling and sound generators, apart from the investment of time required to follow the tailor-made protocol. Reimbursement by national health insurance was granted in all four cases after the possible benefits were outlined by an audiologist from the audiological center. A prospective trial with a standardized multidisciplinary treatment protocol to establish efficacy may be considered in the future.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

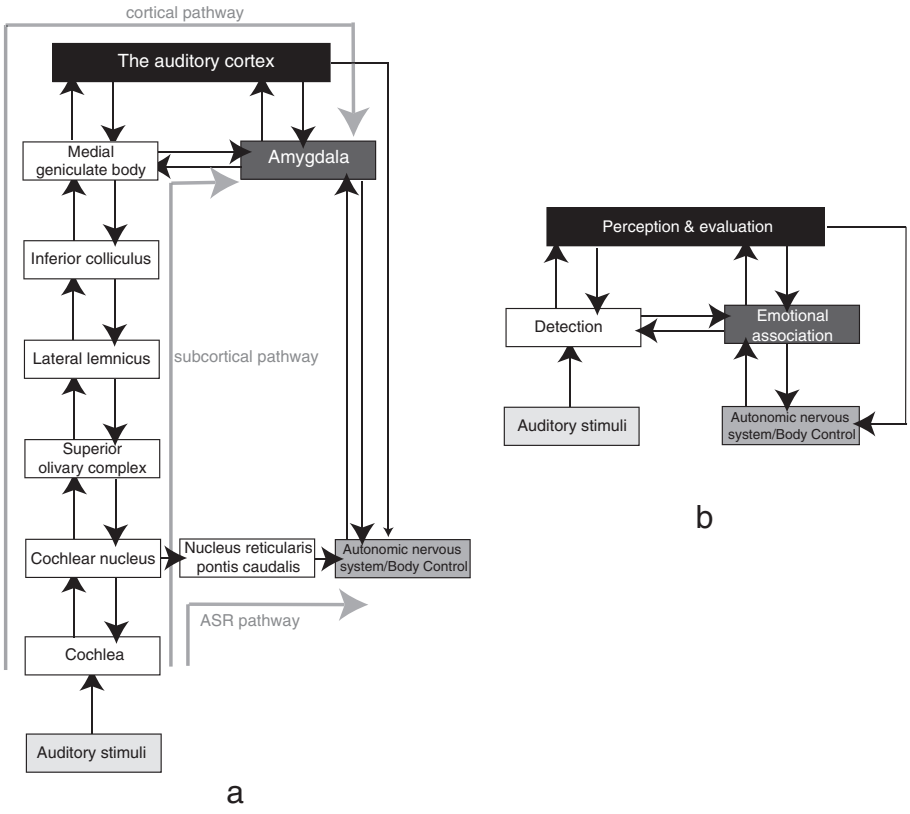

Fig. 1. a) Neural pathways involved during emotional response on auditory stimuli. Note a direct and indirect pathway to the amygdala. b) The Jastreboff Neurophysiological Model of Tinnitus (1995).

Disclosure

None of the authors has any conflict of interest to disclose.

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