

Case Report



A Case Report on Red Ear Syndrome with Tinnitus Successfully Treated with Transcranial Random Noise Stimulation

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Background: The red ear syndrome represents a rare symptom complex consisting of auricular erythema associated with painful and burning sensations. It has been described in combination with tinnitus rarely. It has been hypothesized to be etiologically related to altered trigeminal afferent input, temporomandibular disorders, and thalamic dysfunction.

Objectives: The initial objective of applying transcranial random noise stimulation (tRNS) in a case of red ear syndrome in combination with tinnitus was the alleviation of the phantom sounds.

Study Design: This is a case report on the successful treatment of red ear syndrome with tinnitus by means of transcranial random noise stimulation (tRNS) and a short review on the published cases of this condition.

Setting: We present the case of a 50-year-old woman reporting a simultaneous onset of constant left-sided tinnitus and feelings of warmth accompanied by an intermittent stabbing and/or oppressive pain stretching from the ipsilateral ear to the head/neck/shoulder region, occasionally accompanied by nausea/vomiting and dizziness. After failure of pharmacological treatment attempts, either because of lacking clinical effects (gabapentin, zolmitriptan, and indomethacin) or because of adverse reactions (pregabalin), the patient was offered an experimental neuromodulatory treatment with bitemporal tRNS primarily targeting the tinnitus complaints of the patient.

Methods: tRNS was conducted in 2 – 3 day sessions (stimulation site: bilateral temporal cortex/2.0 mA/10 s on-and-off-ramp/offset 0 mA/20 min/random frequencies 101 – 640Hz / NeuroConn Eldith DC-Stimulator plus).

Results: In 3 consecutive pain attacks repeated sessions of tRNS resulted in substantial alleviation of pain intensity and a prolongation of the interval between attacks. This was an expected finding as the proposed tRNS treatment was initially offered to the patient aiming at an alleviation of the tinnitus complaints (which remained unaffected by tRNS).

Limitations: The reported data derive from compassionate use treatment in one single patient. Application of a sham condition would have been desirable, but is not possible in the context of compassionate use treatment. Nevertheless, we would consider it rather unlikely that the reported effects are purely unspecific as the patient did exclusively report symptom alleviation of pain-related parameters without affecting the tinnitus.

Conclusions: This case report demonstrates the feasibility and therapeutic potential of applying neuromodulatory treatment approaches in red ear syndrome, a rare form of trigemino-autonomal headache. Therefore, it deserves detailed observation in clinical routine applications as well as controlled trials further investigating its neurobiological effects.

Key words: Red ear syndrome, pain, trigemino-autonomal headache, chronic tinnitus, transcranial electrical stimulation, random noise stimulation

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Red ear syndrome (RES) was first described in 3 patients by J.W. Lance in 1994 (1) and was termed "red ear syndrome" in 1996 (2). It has been described to be characterized by the attack-like occurrence of erythema, edema, and dysesthesia of one, or less frequently, of both (3) ears. Most of the patients report a burning sensation, very rarely it has been reported to occur in combination with tinnitus (4,5). Since its first description in the mid 90s, approximately 90 patients have been referred to in the literature with varying presentations (for an overview of all published cases from 1996 to 2010 see [6]). Donnet and Valade {need a reference} proposed a distinction between 2 different types of RES: a) an idiopathic form more commonly reported in young people and frequently associated with migraine; and b) the secondary RES occurring more frequently in elder adults in association with cervical disorders. Other associated pathologies include Chiari I malformation, herpes zoster virus infection of the C3-C6 dermatomes, and exercise-induced compression of the cerebellar tonsils (7). In addition, an association with primary headache disorders including migraine, chronic paroxysmal hemicrania (CPH), hemicrania continua (HC), and short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome has been reported suggesting pathophysiological involvement of cranial autonomic pathways (8). Treatment of RES is difficult; several therapeutic approaches have been tried, but none has proven highly efficient and many patients remain treatment resistant (8).

Case Report

In 2011 a 46-year-old woman presented to our Interdisciplinary Tinnitus Center and reported that she had been suffering from chronic tinnitus since 3 years ago. The whistling sound in her left ear had started accompanied by feelings of heat in the left auricular region together with a stabbing and oppressive pain stretching from the ear to the head/neck, mandibular, and shoulder region strictly limited to the left body side. The tinnitus was described as permanent and non-pulsatile sound perception in the high frequency range (8.400 Hz); the Minimal Masking Level (MML) was measured at 49 dB. Pure tone standard audiometry, speech audiometry, tympanometry, and stapedius reflexes revealed normal results. High frequency audiometry showed a moderate decline reaching a maximum hearing loss of 40 dB (14 kHz) at the right and

50 dB (14 kHz) at the left side. Tinnitus Questionnaires demonstrated a moderate level of handicap (THI 34 [9], TQ 29 [10], Beck Depression Inventory [BDI] 6 [11]). The stabbing peri-auricular pain sensation of attack-like character occurred about twice a month and lasted usually one week. The pain was occasionally accompanied by nausea, with or without vomiting, and dizziness. There was no psychiatric co-morbidity, but the patient reported disturbed sleep (particularly difficulties in fall asleep after waking up during the night) and impaired concentration capacities. Because of her health impairment, the patient had already reduced her work load as a management assistant to 25 hours per week.

At the initial presentation, the patient reported a heating sensation of the left ear and the investigation showed erythema and moderately elevated temperature of the left ear. The medical history revealed a sternotomy more than 25 years ago due to a chest tumor and a hysterectomy. The patient denied regular medication intake, but reported nicotine consumption of about 10 cigarettes/day. Her orthopedic specialist had diagnosed an upper cervical spine syndrome. Regular physiotherapy had no significant effects on pain intensity/frequency and tinnitus levels. A cranial magnetic resonance image (MRI) 2 years before the onset of the tinnitus turned out normal and revealed no hint for a micro vascular compression syndrome. Standard laboratory examinations and electrocardiography did not reveal any significant pathologies.

As a first step we recommended trying indomethacin and zolmitriptan (inhal.) both alone and in combination. These medications did not exert any beneficial effects, but had presumably caused a severe attack of nausea, pain attacks, and vertigo after 5 days, which led to discontinuation of the drugs. The next therapeutic attempt (pregabalin in a dosage of up to 600 mg/day) led to a significant reduction of pain attack frequency (attack-free intervals extended from 3 – 4 weeks to 6 – 7 weeks), but a certain "baseline pain activity" and the tinnitus remained unchanged. After 6 months the dental enamel of the patient started to diminish, which led the dentist to the suspicion of a cancer or adverse drug reaction. As gynecologic examinations, abdominal sonography, and x-ray of the thorax were normal, pregabalin was discontinued and suspected to have caused the enamel reduction, as enamel regenerated after discontinuation of pregabalin. A further attempt with gabapentin did not result in a similar symptom reduction regarding pain attack frequency and tinnitus-related discomfort and was therefore discontinued. Comple-

mentary treatment attempts including traditional Chinese medicine, acupuncture, acupressure, and bioresonance treatment had no influence on the symptoms. Dietary changes (reduction of pork and carbohydrates) reduced nausea and vomiting during the headache attack, but had no influence on the pain intensity.

Based on a case report on the application of transcranial random noise stimulation (tRNS), an innovative form of transcranial direct current stimulation (tDCS), in neuropathic pain (12) and promising results of tRNS for treatment of tinnitus (13,14), compassionate use treatment [\[what is compassionate use treatment?\]](#) with tRNS was proposed to the patient. The patient gave written informed consent after a comprehensive explanation of the procedures.

The treatment consisted of an alternating current stimulation of 2.0mA intensity with a 0 mA offset applied at random frequencies ranging from 101 to 640Hz. The current was transmitted by a saline-soaked pair of surface sponges (5cm x 7 cm) and delivered by a battery-driven, constant current stimulator with a maximum output of 10mA (NeuroConn Eldith Stimulator plus; <http://www.neuroconn.de/>). The stimulation was targeted to the bilateral auditory cortex. The inferior middle parts of the saline-soaked sponge electrodes were placed on the T3 and T4 spot as determined by the International 10/20 Electroencephalogram System. Current intensity was increased in a ramp-like fashion over 10seconds until reaching 2.0mA and stimulation was maintained for a total of 20minutes (terminated with an off-ramp of 10 seconds).

The first treatment with tRNS was started on the third day of a pain attack, normally lasting for about one week, and she reported immediate symptom alleviation the day after the initial treatment session. Usually pain attacks took place quite regularly with an interval of more or less 3 weeks.

Five weeks later the next pain attack occurred. In this pain attack tRNS was started on the second day and repeated on 2 consecutive days. After this treatment series, the patient was completely relieved from headaches including her "baseline pain," which had been present for 6 years since the initial onset of the syndrome. No adverse effects were noticed. Baseline pain returned after a short period of 2 – 3 days.

She returned to our hospital almost 7 weeks later and reported another painful attack starting with concentration problems (as almost always) on a Sunday. Due to the intense feelings of pain, she was not even able to walk without support, but during tRNS stimula-

tion (same parameters as mentioned above), she experienced an immediate alleviation of her pain sensation exactly as during the previous treatment. After day 2 she was completely relieved from pain, after day 3 she reported an alleviation of her feeling of exhaustion and drowsiness, showing the same pattern as during the previous tRNS treatment. The patient reported that an interval of 7 weeks without pain attacks was very unusual for her; normally she had suffered from a pain attack at least once in a month (usually lasting for a whole week). Analogously to the preceding stimulations, the patient initially experienced a complete pain relief with a return of her baseline pain after a short period of 2 – 3 days.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

DISCUSSION

A brief historical and technical overview of transcranial electro-stimulation (tES): Based on the observation of Bindman and colleagues (15) in 1964, that stimulation with electrical currents may modulate the spontaneous neuronal activity in the rat brain, a variety of studies focused on the application of electrical currents in animals and humans during the late 1960s and 1970s. Due to the emphasis on psychopharmacological treatment approaches in the aftermath, this treatment approach has not been consistently expedited until Nitsche and Paulus (16) rediscovered it in 2000, demonstrating a differential effect of anodal and cathodal tDCS on motor cortical excitability. During the last years tDCS and other forms of transcranial electro-stimulation (tES) have gained increasing attention as potentially promising innovative treatment approaches for a variety of neuropsychiatric diseases. tES-based approaches may be divided into transcranial direct current stimulation (tDCS) applying electrical currents up to 2 mA, transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS). tDCS is the most systematically investigated approach and its modulating effects in the human brain could be reliably quantified by applying motor evoked potentials (17-22). The method is apt to modulate the neuronal resting membrane threshold and thus diminishes or enhances the probability for a depolarization of neurons and the occurrence of an action potential (23). With its continuous stimulation character, tDCS is almost painless and can be easily investigated in double-blinded placebo-controlled protocols.

tRNS as innovative form of electrical current stimulation: tRNS is based on the application of alternating currents of random polarity with a frequency between 0.1 and 640 Hz (24) and was introduced to the scientific community in 2008 (25). It is hypothesized that by the random changes in polarity homeostatic counteracting processes influencing the neuronal ion channels in the electrical field are avoided thus inhibiting adaptation processes of the neuronal cell membrane and the resulting back shift to "resting state"-levels (24). High frequency tRNS (101 – 640 Hz) exerts excitatory cortical effects of the motor cortex (26) and the auditory cortex (27), whereas low frequency tRNS (0.1 – 100 Hz) seems to exert no significant effects on motor cortical areas (25). However, clinical effects of low-frequency tRNS applied to the auditory cortex have been shown in chronic tinnitus (28). With regard to adverse effects, tRNS seems to be tolerated with a lower rate of skin irritation compared to classical tDCS (29,30), probably because of balanced charges in tRNS as compared to tDCS.

tDCS and chronic pain: Only a few studies are currently available with regard to tDCS treatment in chronic pain conditions. Most of them focus on the stimulation of the motor cortex and – concerning migraine – the visual cortex (31). The inhomogeneity of the applied stimulation parameters and targets may be due to inconsistent findings of interictal excitability changes in migraine patients that have been reported to be both hypo- and hyper-excitabile (32).

Da Silva {in the references, this is spelled Dasilva, which is correct?} et al (33) published the results of a sham-controlled trial in 13 patients with chronic migraine examining the prophylactic effects of anodal tDCS of the primary motor cortex, demonstrating significant effects on intensity and duration of the headaches. Another study on migraine prophylaxis showed a significant reduction of attack frequency, intensity, and medication intake by left-sided M1-tDCS in 37 patients (actively treated: 20) in contrast to sham-stimulation (34). Antal et al (35) showed an inhibitory effect of cathodal tDCS of the visual cortex in chronic migraine in 26 patients based on the assumption of a hyper-excitabile cortex in symptom-free intervals in chronic migraine. Patients reported a reduction of migraine duration, episode count, and intensity (the latter significantly differing from sham-stimulation). A clinical study by Baschi et al (36) {why not reference Baschi et al directly?} reported preliminary results concerning cathodal (inhibitory) tDCS of the visual cortex in 20 patients suffering of chronic migraine by left DLPFC stimulation

over 8 weeks (20 minutes daily) for the activation of anti-nociceptive top-down regulatory mechanisms: after 2 months of treatment there was a 43.7% reduction ($P = 0.05$) of severe migraine attacks and a reduction of cumulative headache-time by 30.2% ($P = 0.02$). In another recent study (37), 19 patients with migraine were treated by cathodal tDCS of the visual cortex in 12 sessions. The stimulation led to a significant reduction of attack frequency, medication intake, and episode duration, but – contrasting previous hypotheses – no excitability changes could be observed after tDCS treatment (37). In contrast to these approaches, Vigano et al (36) showed a preventive effect of 8-weeks' excitatory (anodal) tDCS of the visual cortex in 10 patients with episodic migraine.

Taken together, the currently available studies regarding tDCS in headache disorders suggest a beneficial effect of anodal tDCS in episodic migraine and cathodal tDCS in chronic migraine (31). The effects and underlying neurobiological changes associated with migraine disorders are to be elucidated in the future with more detail.

tRNS and pain: A pubmed search on July 17, 2015 (search terms: tRNS AND pain), resulted in one hit. Alm and Dreimanis (12) reported a case series of 4 patients suffering from neuropathic pain successfully treated in a cross-over-sham controlled pilot study. Surprisingly, the effects were registered even at low stimulation intensities (100 μ A), and very short treatment intervals (up to 30 seconds). Regarding RES or chronic migraine, no data are currently available.

Red Ear Syndrome: Two years after its first description in 1994 (1), the same author described a larger group of 12 patients and their symptoms, ultimately terming it "red ear syndrome" (2). The symptoms were characterized by the presence of attack-like unilateral pain experiences during which the involved ear becomes red and burning. Ten out of the initially described 12 patients suffered from upper cervical arachnoiditis, cervical root traction, cervical facet joint spondylosis, glossopharyngeal and trigeminal neuralgia, temporomandibular joint dysfunction, and thalamic syndrome (38). Among the about 90 published cases of RES, 60% are about women and 40% are about men (6,38). In only 2 cases has RES been described to be accompanied by chronic tinnitus in the literature: in the first one in 2011, the authors only stated "Bilateral tinnitus and migraine without aura were secondary complaints" without any further explanation or characterization of the phantom percept (5). Notably, migraine episodes (twice a month)

were not directly associated with the RES attacks in this patient (5). A second case of RES and accompanying tinnitus was reported by Chan and Ghosh in 2014 (4): The authors described the case of a 22-year-old woman who presented twice in a department of neuro-otology with a temporal delay of 5 years. At the first consultation she reported bilateral hyperacusis (abnormal sound sensitivity arising from within the auditory system to sounds of moderate volume, which would not trouble other people), intermittent right-sided tinnitus, and subjective hearing difficulties. Five years later she presented with highly distressing episodes of erythematous ears, which were associated with burning pain around the ear and temporal areas, and intolerance to noise. At the first presentation, she also reported right ear fullness and significant difficulty hearing in background noise when stressed. Otoscopy, a neurological examination, pure-tone audiometry, tympanometry, stapedial reflexes, oto-acoustic emissions, auditory brainstem response, and speech audiometry results were normal. When presenting again due to the RES symptoms 5 years later, she denied symptoms like tinnitus, nausea, visual field symptoms, or vertigo, but reported a persistent hyperacusis that was exacerbated during the painful RES attacks (4). To our knowledge, no data exist concerning a simultaneous onset of RES symptoms and tinnitus as described in our case report (see above). As in both other case reports describing RES and tinnitus, the clinical complaints of our patient were associated (but not specifically temporarily coupled) with migraine comorbidity (4,5). The close interaction of RES and cervical or temporomandibular joint disorders (38) might provide an explanation for the co-existence of RES and tinnitus in this patient. Altered somatosensory input has been suggested as a trigger or contributing factor for tinnitus generation since the late 90s (39,40). Moreover, it has been suggested that the presence of altered somatosensory input and cross-modal afferent activation in the dorsal cochlear nucleus might represent a defining issue for a specific subtype of chronic tinnitus requiring specific therapeutic management (41,42).

Discussion of treatment effects in our patient: The exploratory treatment attempt described above was inspired by promising reports of successful treatment of chronic tinnitus by means of tRNS (13,14). Surprisingly, the sound perception of our patient did not change during the course of 3 treatments, but she reported immediate and pronounced reductions of her pain episodes. The improvement in pain intensity was

consistently repeated with an immediate alleviation during the initial session, a complete pain cessation on day 2, and consolidation on day 3. Immediately after the stimulation, the patient was completely free of pain including her "baseline-pain" (for an interval of 2 – 3 days). Usually, her pain attacks last for more or less 7 days and the patient had been used to not planning anything after a period of 3 – 4 weeks expecting the next "week off." In the course of the treatment, she reported a prolongation of the periods free of pain attacks up to 7 weeks (almost double the usual time) with a lack of longer lasting effects on her "baseline pain" that had been present since the beginning of the symptomatology. The isolated therapeutic effect on "pain attacks" without affecting the patient's chronic tinnitus may lead to the postulation of a specific effect of tRNS on pain pathophysiology. It further remains to be elucidated if tRNS in this condition exerts its effects by an alteration of peripheral trigeminal afferents or by a direct effect on central neuronal activity (or by a combination of both).

Whereas both trigeminal and intracranial neuromodulation have been investigated for migraine and trigeminal autonomic cephalgia, much better evidence is available for extracranial stimulation (43), suggesting that the peripheral effects of tRNS treatment may have been more relevant for headache reduction in our patient. Given the fact that tRNS has been reported to increase neuronal excitability (27), the question of the meaning for the pathophysiological underpinnings of RES remains open.

Apart from that, we are well aware of the limitations of our report as the data come only from compassionate use treatment in one single patient. Application of a sham condition would have been desirable, but is not possible in the context of compassionate use treatment. Nevertheless, we would consider it rather unlikely that the reported effects are purely unspecific as the patient did exclusively report symptom alleviation of pain-related parameters without affecting the tinnitus. Moreover, the prolongation of pain-free-intervals might serve as a further argument against unspecific treatment effects as placebo effects are typically known to diminish over time and the patient had not experienced beneficial effects of several other pharmacological treatment options before. Due to the exploratory character of our treatment attempt, it remains unclear at the moment whether the effects might be enhanced by selecting other stimulation parameters or targets. It would be highly desirable to identify the un-

derlying mechanisms of action of tRNS in the treatment of RES in a more detailed manner and a larger cohort of patients.

CONCLUSION

In consideration of the very limited current knowledge both on the neurobiological underpinnings of RESy and the therapeutic potential of tRNS in this condition (and associated symptoms such as chronic pain, migraine, chronic tinnitus, etc.), our case report is remarkable, as it represents the first description of successful treatment of RES utilizing an innovative and up-coming neuromodulatory treatment such as tRNS. tRNS in our opinion is especially attractive as an innovative therapeutic option in such cases with divergent pathophysiological findings and theories underpinning the clinical symptoms due to several issues: a) based on its charge-balanced character, it is not as necessary as in tDCS-based approaches to initially figure out stable excitability changes in clinical conditions; b) the absence of net electrical current flow very likely represents the

reason for excellent tolerability (even better than in tDCS in our experience); and c) based on its wide-spread neurobiological effects and large-sized electrode configuration, a targeted approach is feasible without the essential requirement of high target focality required in other neuromodulatory stimulation techniques such as transcranial magnetic stimulation (TMS). Therefore, it may hold significant therapeutic potential and deserves further observation in clinical routine applications as well as controlled trials further investigating its neurobiological effects.

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