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Detection of bacterial DNA on neurostimulation systems in patients without overt infection

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ABSTRACT

Objective: Hardware-related infection remains a major problem in patients with neurostimulation systems. The role of bacterial colonization and the formation of biofilm on the surface of implanted devices remain unclear. Here, we analysed the incidence of bacterial DNA on the surface of implantable pulse generators (IPGs) using 16S rRNA gene sequencing in a consecutive series of patients who underwent routine IPG replacement without clinical signs of infection.

Patients and methods: We included 36 patients who underwent scheduled replacement surgery of 44 IPGs. The removed IPGs were processed and whole genomic DNA was extracted. The detection of bacterial DNA was carried out by Polymerase Chain Reaction (PCR) using universal bacterial primers targeting the 16S rRNA gene. The DNA strands were analysed by single-strand conformation polymorphism (SSCP) analysis.

Results: Indications for chronic neurostimulation were Parkinson disease, tremor, dystonia, neuropathic pain and peripheral artery occlusion disease. Mean age of patients at the time of implantation was 48 ± 17.6 years. The mean interval between implantation and replacement of the IPG was 24.8 months. PCR/SSCP detected bacterial DNA of various species in 5/36 patients (13.9%) and in 5/44 pacemakers (11.4%), respectively. There was no evidence of clinical infection or wound healing impairment during follow-up time of 45.6 ± 19.6 months.

Conclusion: Bacterial DNA can be detected on the surface of IPGs of neurostimulation systems in patients without clinical signs of infection by using PCR techniques. It remains unclear, similar to other permanently implanted devices, which mechanisms and processes promote progression to the point of overt infection.

1. Introduction

Neuromodulation via chronically implanted neurostimulation systems has become an accepted therapeutic option in a variety of disorders [1–7]. In particular, deep brain stimulation (DBS) for the treatment of movement disorders and spinal cord stimulation (SCS) for neuropathic pain are considered now standard treatment worldwide [8–10]. While there has been tremendous progress in technology over the past two decades, hardware-related complications remain a major issue with infection being one of the most distressing problems.

The frequency of infections in patients with implanted neurostimulation systems has been reported to range between 1% and 22% [9,11–22]. This wide variability is not only due to different definitions of what constitutes an infection but also to the patient's general condition and probably the underlying disorder and other risk factors [19,21,23]. Infections may manifest as chronic wound healing problems, skin erosions with or without purulent discharge or wound dehiscence with exposure of the foreign material [12,19,24–27]. Hardware-related infections may occur anywhere along the implanted material, but are found most frequently at the pocket of the implantable pulse generator (IPG) or at the connection site between the implanted electrode and the connecting cable [19,28,29]. One study found that the risk for hardware infection is greater at IPG replacement surgery than at the time of the primary procedure [30].

The high proportion of infection in patients with neurostimulation systems may be related to bacterial colonization and the formation of biofilms on the surface of implanted devices [31–33]. However, it remains unclear, whether patients without infection might have

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harboured bacterial colonization on the surface of their neurostimulaton systems and how often asymptomatic bacterial colonization is encountered. Here, we analysed the presence of bacterial DNA on the surface of 44 IPGs by detection of bacterial DNA using 16S rRNA gene sequencing in a consecutive series of 36 patients without clinical signs of infection. Further, patients were followed to investigate whether detection of bacterial DNA would predispose to subsequent infection after pacemaker replacement.

2. Patients and methods

2.1. Study design

Patients with neurostimulation systems without clinical signs of infection who underwent scheduled IPG replacements for battery exhaustion during a 1-year study period were considered for this study. Exclusion criteria were: clinical signs of hardware-related infections, other infectious disorders and current antibiotic therapy. While 28 patients had a single IPG which was replaced, 8 patients had bilateral IPGs which were removed during the same procedure.

The initial implantation of DBS or SCS systems was performed as described in detail elsewhere [34,35]. All patients had prophylactic intravenous antibiotics prior to skin incision at the first surgery which was continued for 48 h postoperatively. Cephalosporins were used in 35 patients and amoxicillin in one instance. Skin incisions were conducted in a way that all prominent elements of the neurostimulation systems were covered by intact skin. In patients with DBS the IPGs were implanted in a subclavicular subfascial pouch, and in patients with SCS in a subcostal subcutaneous pouch.

The manufacturer of all neurostimulation devices was Medtronic (Medtronic Inc., Minneapolis, USA).

2.2. Device removal

Upon replacement of the IPGs the wounds were swabbed and draped aseptically. Standard desinfection was performed with mecetronium ethylsulfate solution (Sterilium®) and povidone-iodine solution (Braunoderm®). After opening of the previous skin incision along the scar, the fibreous tissue pocket was dissected and the IPG was removed carefully.

After removal, the IPGs were stored at −80 °C in sterile single use plastic bags for further analysis. Subsequently, swabs were taken with sterilized foam pellets (ORBIS Dental, Münster, Germany) at different sites of the device surface.

2.3. DNA preparation

Procedures for genomic DNA extraction as well as 16S rDNA amplification, purification and analysis via single strand conformation polymorphism (SSCP) and sequencing were described in detail previously [36]. In summary, we applied a 16S rRNA-targeting PCR method to detect bacterial DNA. Swab samples were treated with a lysis buffer of 20 mg/ml lysozyme solution in 20 mM Tris HCl, 2 mM EDTA, 1.2% Triton X100, pH 8.00 for 30 min at 37 °C, followed by proteinase K digestion. The suspension then was homogenized by sterile 0.5 mm glass beads in a Precellys 24 bead mill (6500 rpm). Subsequently, whole genomic DNA was purified with the QIAmp® DNA Mini Kit (Qiagen GmbH, Hilden, Germany) according to the standard protocol for purification of bacterial genomic DNA.

2.4. Polymerase chain reaction and further analysis

Amplification of 500-bp fragments was performed using universal primers targeting hypervariable regions within the bacterial 16S rRNA gene [37]. PCR was conducted as described by Heuer et al [38]. From the PCR product single-stranded DNA (ssDNA) was generated by digestion with 10 U lambda exonuclease and purification using the QIAquick PCR Purification Kit (Qiagen, Hilden, Germany). Resulting single-stranded 16S rDNA fragments underwent single-strand conformation polymorphism (SSCP) analysis on a DCode Universal Mutation Detection System (Bio-Rad, Hercules, USA). Electrophoretical separation of the ssDNA fragments was achieved on a 10% polyacrylamide gel at 350 V (20 °C) in 1x TBE buffer (Bio-Rad, Hercules, USA) for 24 h. Silver-staining (Silver-Stain kit; Bio-Rad, Hercules, USA) was used to visualize DNA bands [39]. Subsequently, DNA bands were extracted from the gel, homogenized and nucleic acids were eluted overnight at 50 °C, concentrated by ethanol precipitation and resuspended in double distilled water prior to PCR re-amplifications and Sanger sequencing. The BioEdit software package (v7.0.9, Ibis Biosciences, Carlsbad, USA) was used for sequencing analysis. The results were compared to GenBank database from the National Center for Biotechnology Information (NCBI) for taxonomic classification [40].

3. Results

In the 36 patients included in this study, the primary indications for the initial implantation of a neurostimulation system were Parkinson disease (n = 3), tremor (n = 4), dystonia (n = 18), neuropathic pain (n = 9), and peripheral artery occlusive disease (n = 2). A DBS system was implanted in 26 patients, a SCS system in 9 patients, and a neurostimulation system for peripheral nerve stimulation in one patient. There were 22 women and 14 men. Mean age at the time of the implantation of the neurostimulation system was 48 ± 17.6 years (range 15–76 years).

The mean interval between the implantation of the neurostimulation system and replacement of the IPG was 24.8 ± 14.9 months (range 5–66 months).

Bacterial DNA of various bacterial species was detected in a total of 5 patients (5/36 corresponding to 13.9%). When considering the number of replaced IPG, the frequency of positive results was 11.4% (5/44).

Our analysis detected DNA of *Staphylococcus epidermidis*, mixed *Lactobacillus iners* and *crispatus*, or *Bacillus species*, in one patient each, respectively. Furthermore, bacterial DNA was found on the surface of the device in two other patients, however, the detailed spectrum of germs was not identifiable in the sequencing analysis.

The mean follow-up after replacement surgery was 45.6 ± 19.6 months. One patient was lost to follow-up during that period. There was no evidence of clinical infection or wound healing impairment in any patient.

4. Discussion

Our study shows that bacterial DNA can be found in patients with implanted neurostimulation systems who do not display overt signs of infection. The detection of bacterial DNA may indicate both current and former bacterial colonization with bacteria. Such bacteria might have been unable to survive or to multiply under certain conditions. Our results are in line with previous studies on patients who underwent replacement of cardiac pacemakers or of other implanted devices [31,41,42]. Bacterial DNA, for example, was detected by PCR on the surface of the devices in 29.7% of patients without symptoms in a series of a total of 118 patients with cardiac pacemakers [31]. Remarkably, while none of our patients developed clinical signs of infection during follow-up after replacement of the IPG, three patients became symptomatic with the same microorganisms during follow-up in the series of cardiac patients [31]. Such findings, of course, raise the question which circumstances promote the development of subsequent infection from asymptomatic bacterial colonization on the surface of implanted devices.

Although it has been commonly accepted that biofilm formation secondary to bacterial colonization might underlie the subsequent

development of infection, the mechanisms still remain unclear (19). The relevance of different risk factors for the development of overt infection in patients with implanted neurostimulation systems is poorly understood. There are conflicting data about age, the length of surgery, the type of skin incision, and patient-specific factors such as smoking, obesity and diabetes mellitus [14,18,19,21,24], which have been suggested to increase the risk for infection in patients with implanted neurostimulation systems. It has also been reported that a diagnosis of Parkinson disease would predispose to more frequent infections, while on the other hand it has been observed that new indications, in general, would present a possible risk [11,17,20,26,27].

According to a recent systematic review of hardware-related complications of DBS, the most frequent pathogen which was identified from wound cultures was *Staphylococcus aureus*, which was detected in up to 20% of patients, while other pathogens were evident in about 13% [10,11,14,17–19]. Other pathogens that are commonly found with infections of neurostimulation systems include *coagulase-negative Staphylococcus*, *Staphylococcus hominis*, *Staphylococcus epidermis*, and common skin flora [19,11,14].

PCR techniques have a very high sensitivity to detect bacterial DNA [31,43,44]. The use of PCR techniques practically allows detection of virtually all bacteria, and subsequent sequencing may yield final identification. The specific problems of PCR techniques to detect bacterial DNA with negative results in culture have been discussed before [45]. As in other previous studies, without a more precise quantitation of nucleic acid load it is difficult to exclude completely that potentially false-positive results are being produced due to contamination during collection of samples, handing of the probes, and also during PCR processing. Although utmost care was applied to avoid any contamination while handling the devices in our study, secondary contamination cannot be completely excluded. An option for future studies would be to perform PCR in addition from the outside surface of the surgical gloves which was used to obtain the specimens.

The reason for lack of a detailed germ spectrum in two of our patients, despite clear evidence of bacterial DNA, is probably due to the fact that the primers in our essay did not bind on all 16S rRNA genes in a completely uniform manner. Similar limitations have also been reported in multiplex PCR assays used for the early diagnosis of ventriculostomy-related infections [45].

A large body of evidence has become available for bacterial colonization of suture material [36,46–48]. Bacterial colonization has been demonstrated in various experimental and clinical studies [46,49–51]. In a recent study we demonstrated that the DNA of various bacteria species could be detected on suture material in 10/ 38 patients with well healed wounds, while this was the case in 12/ 25 patients with wound healing impairment upon revision surgery in various neurosurgical procedures. We concluded that suture material may provide a nidus for bacteria and subsequent biofilm formation, however, that such colonization would not be a general primer for subsequent wound infection.

While our present study demonstrates that bacterial DNA may be detected on the surface of IPG in a certain percentage of patients with implanted neurostimulation systems and asymptomatic wounds, several questions remain unanswered. It may well be that there exists an equilibrium in some patients between the human host and bacterial device colonization [31,33]. Only when this balance is disturbed, the process might progress to overt clinical infection. Future studies need to clarify the exact mechanisms and processes that are involved, and whether impregnation of IPG or the local application of antibiotics would be useful to prevent both bacterial colonization and overt infection.

5. Conclusion

Bacterial DNA can be detected on the surface of IPGs of neurostimulation systems by using PCR techniques in patients without signs of infection. The detection of bacterial DNA may indicate both current and former bacterial colonization with bacteria. It remains unclear, similar to other chronically implanted devices, which mechanisms and processes lead to progression to the point of overt infection.

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