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Auditory brainstem implantation in primates: lessons for human surgery and application

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Abstract

We report on the surgical technique for surface electro-auditory prosthesis (EAP) implantation, pathological changes occurring at the cochlear nucleus complex (CNC), and its relation with electrical stimulation. Fourteen *Macaca fascicularis* were operated upon for a translabyrinthine bilateral auditory neurectomy, and simultaneous unilateral EAP implantation. Six animals were not stimulated, and the remaining eight were connected to an external active device. Stimulation was planned for 1000 hours. Biotolerance to the materials was adequate without significant reactions in the CNC surface, but an ependymal reaction. Lesions attributed to surgical trauma were also found. Two animals being stimulated could not complete the planned course due to cable break or EAP extrusion. One stimulated animal developed an asymptomatic brainstem abscess. A good knowledge of CNC topography is required to avoid surgical trauma. Externally connected devices may facilitate extrusion of the EAP or ascending infections.

Key words: Primates; Cochlear Nucleus; Pathology; Rehabilitation of Hearing Impaired; Brain Stem; Prosthesis Implantation

Introduction

Ongoing clinical trials suggest that auditory brainstem implants (ABI) may be an appropriate palliative treatment for patients with bilateral profound sensorineural hearing loss due to a cochlear nerve lesion.[1] In 1995 an experimental study was started in non-human primates, in co-operation with Cochlear Ltd., in order to investigate the effects of auditory deafferentation, changes after ABI implantation, and changes after electrical stimulation. The ABI used was placed on the surface of the cochlear nucleus complex (CNC). Partial results of these investigations have been published recently.[2,3] The purpose of the present paper is to show the findings on the surgical technique of implantation, and to correlate them with pathological findings. These will permit us to improve our technique and results.

Materials and methods

(1) Animal model

Fourteen adult male captive-bred *Macaca fascicularis* were used, ranging from 1.9 to 3.2 Kg in weight (mean 2.6 Kg.). As controls, several normal and bilaterally deafferented animals prepared for previous studies (referred to as *groups A* and *B*) were used. Experimental animals were placed into two groups according to the aims of the study:

Group C: six animals undergoing a bilateral VIIIth cranial nerve neurectomy and simultaneous unilateral ABI implantation; the ABI was placed on the surface of the CNC and was not electrically activated, remaining in place for three months.

Group D: eight animals undergoing a bilateral VIIIth cranial nerve neurectomy and unilateral ABI implantation; the surface ABI was electrically activated.

(2) Housing and care of the animals

The 14 *Macaca fascicularis* used for this study were housed individually in stainless-steel cages (120 × 75 × 100 cm), in a room with controlled temperature (22 ± 1°C), humidity (55 ± 10 per cent) and lighting (0800–2000 h). They were fed commercial non-human primate food, and supplied with fruit daily and water *ad libitum*.

(3) Auditory brainstem implant prototype

Cochlear Ltd (Australia) manufactured the ABI device (Figure 1), in accordance to the specifications given by the research group. The electrode pad was made of medical silicone, slightly elliptically-shaped, and measured 3.8 × 1.6 × 0.6 mm. Surface electrodes were attached to one side, while the other was covered by a 1 cm Dacron mesh for stabilization purposes. The Dacron mesh could be easily cut on demand before implantation. The electrodes were built of platinum and were circular in shape. Two of

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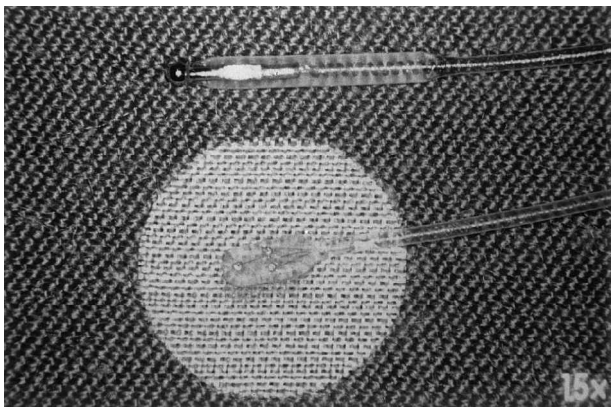

FIG. 1

The surface auditory brainstem implant device containing the three electrodes. Notice the Dacron mesh around the device and the reference electrode.

FIG. 2

The surgeon handles animal wearing the jacket after the procedure; the stimulator is contained in the back pocket.

them were 0.2 mm and the third was 0.3 mm long. In animals from group D, the electrode pad had a cable with an external connection for the stimulator. The ABI was sterilized by ethylene oxide before implantation.

(4) Surgical procedure

A mastoidectomy was performed to reveal the internal auditory canal (IAC), that is in a similar position to that in the human being. The posterior wall of the mastoid cavity was drilled out to expose the dura of the posterior fossa. After section of both vestibular nerves, the auditory nerve was found within the IAC and sectioned. For the ABI implantation, the posterior fossa dura was incised and the flocculus retracted to achieve a complete visualization of the cranial nerves VII and VIII at the brainstem. After identification of the foramen of Luschka and transverse section of the tela coroidea, the lateral recess could be approached. The ABI electrode array was placed medial to the entrance of the VIIIth cranial nerve to the brainstem, with a 30° cranial rotation. The dural defect was closed with a piece of muscle and the labyrinth was sealed with bone wax. In animals from group C, the ABI and cable remained totally implanted, whereas in animals from group D, the cable was taken subcutaneously to the interscapular area and exteriorized by skin incision. Thus, the implant was ready to be connected to the stimulator, which was placed inside a special jacket worn by the animal (Figure 2).

(5) Stimulation

A 12-hour cyclic stimulator was used. Animals from group D were stimulated with different parameters of current and K values. Stimulation data are shown in Table I.

(6) Specimen preparation

Primates were painlessly sacrificed with an overdose of barbiturates three months after surgery, and perfused transcardially for more than one hour with paraformaldehyde in increasing concentration, in phosphate buffer (pH 7.4, room temperature), and ending with five per cent sucrose in phosphate buffer. The skull was carefully removed and the brain placed in an equilibrating solution of glycerol plus DMSO in phosphate buffer until sectioning. The electrodes were left in place; photographs of the brainstem were obtained for orientation and position recording, and were removed afterwards. The brainstem was sectioned at the level of the cerebral peduncles and placed in a freezing microtome, so that orthogonal sections to the main axis of the brainstem could be obtained. Thirty micron serial sections were prepared in all cases with an interval of 240 μm between adjacent sections. Of the 14 series obtained, one was Nissl-stained with thionine for cytoarchitecture and damage evaluation purposes. The remaining series were stored in a cryoprotectant solution until used for immunostaining.

Results

All animals from group C survived three months with the ABI in place before sacrifice. Although we planned 1000 hours of stimulation in animals from group D, this was not achieved in any of the animals because the cable broke at different levels in animals D1, D2, D4, D5, D7 and D8. Also, in animals D3 and D6 there was a complete ABI extrusion before the end of the planned stimulation period.

From the surgical and pathological point of view, the findings were as follows:

TABLE I

STIMULATION DATA.

Animal	D1	D2	D3	D4	D5	D6	D7	D8
Current delivered (mA)	0.40	1	0.26	0.26	1	0.47	NA	1
K value for 0.2 mm	1.38	2.16	0.99	0.99	2.16	1.51	NA	2.16
K value for 0.3 mm	1.13	NA	0.74	0.74	1.99	1.26	NA	1.99
Stimulation time (hours)	216	732	708	468	84	396	0	192

K value is shown separately for the different diameter electrodes. NA = not activated

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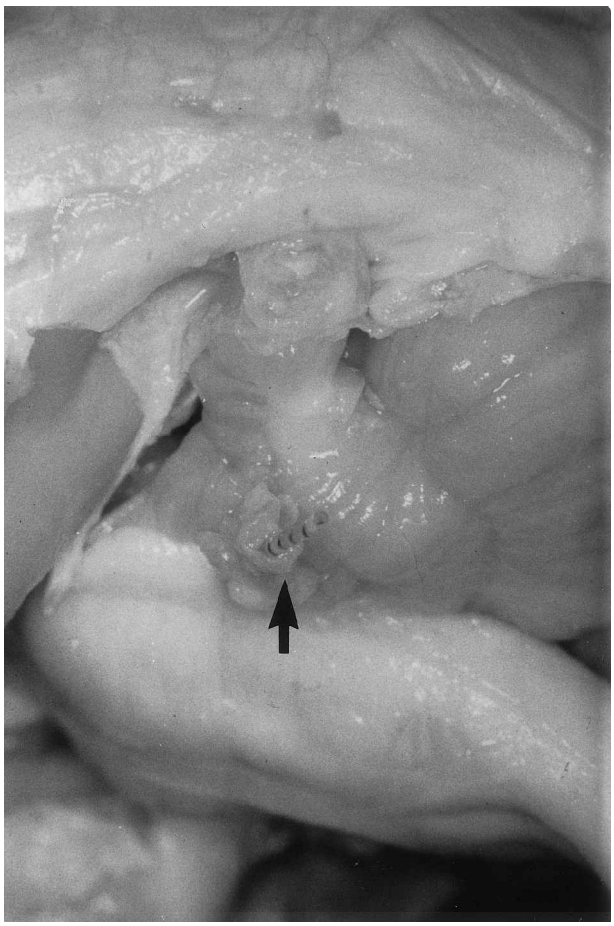

FIG. 3

Lateral autopsy view of the brainstem and cerebellum. The arrow points to the silicone cable wrapped in fibrous tissue.

(1) Lesions on the CNC and brainstem related to surgical trauma

In the first four animals of the group C the dummy ABI was completely introduced within the lateral recess. Histology studies showed penetration to be excessive, medial to the CNC, and too deep into the lateral recess. Primates C1 and C2 presented an almost complete destruction of the CNC due to direct damage during placement of the ABI, because it was placed intraparenchematously and not on the CNC surface. Animals C3 had less destruction of the CNC, but the ABI penetrated deeply into the brainstem up to the inferior cerebellar peduncle.

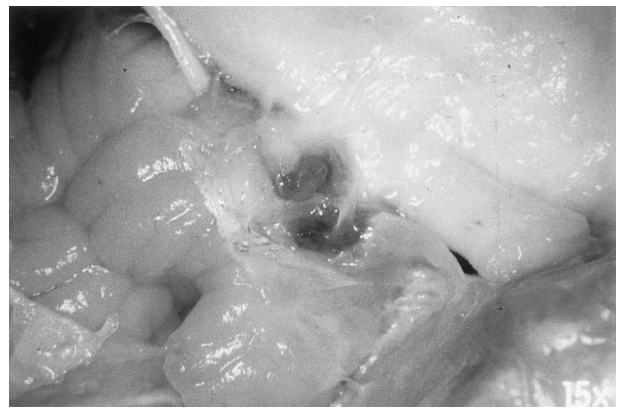

FIG. 5

Lateral autopsy view of a stimulated animal (D5), after auditory brainstem implant removal. The surface of the cochlear nucleus complex appears brownish coloured.

(2) Stabilisation of the ABI

During autopsy the electrode positioning was studied in detail to evaluate an eventual migration of the ABI. In primates from group C, migration of the ABI was not observed in any of the animals. In primates from group D, extrusion of the ABI occurred in two cases (D3 and D6) after 708 and 396 hours of stimulation, respectively. The possible reason for these two extrusion cases is the external connection between the ABI and the stimulator. The traction forces applied to the ABI, due to the weight of the stimulator and the animal movements, led to the subsequent extrusion.

(3) Scar tissue and biotolerance of the materials

Intracranially, at the cerebellopontine angle, during autopsy we found that the silicone cable was wrapped by fibrous tissue (Figure 3), 2.33 to 2.66 mm thick. This capsule had to be opened longitudinally with a scalpel to enter the lateral recess. At this level, a slight fibrous reaction was observed around the

FIG. 4

After partial removal of the fibrous tissue around the cable, the auditory brainstem implant may be detached easily from the brainstem.

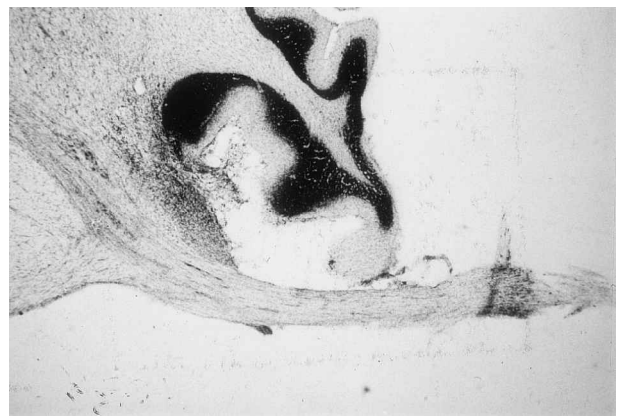

FIG. 6

Nissl stain (×20) of the brainstem of a stimulated animal (D5). A minor pial thickening is observed on the surface of the brainstem.

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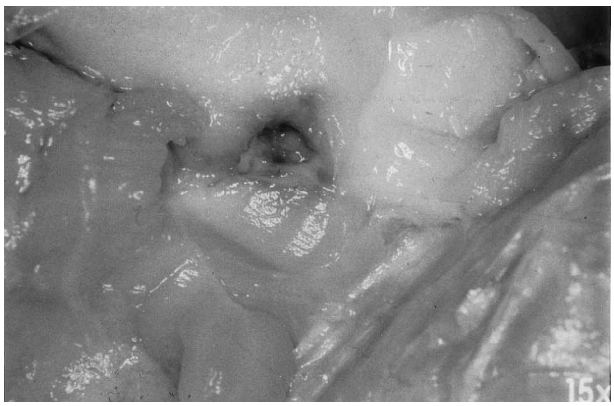

FIG. 7
Lateral autopsy view of a stimulated animal (D8) after auditory brainstem implant removal. A wet lesion was noticed on the surface of the cochlear nucleus complex.

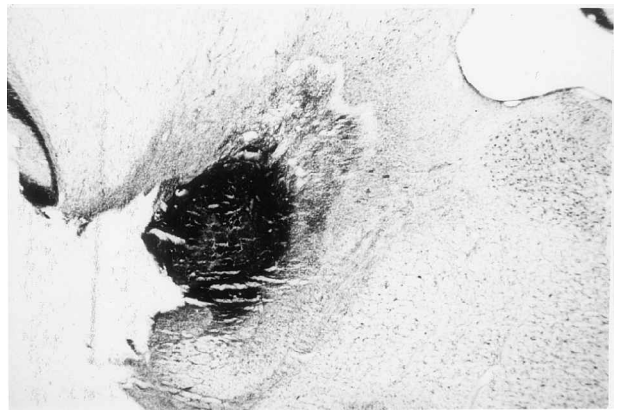

FIG. 8
Nissl stain (×20) of the brainstem of a stimulated animal (D8) with an intraparenchematous abscess at the cerebellopontine angle, and ample destruction of the cochlear nucleus complex.

electrode array. In all the animals, the side of electrodes was easily detached from the brainstem without observable signs of scarring under the operating microscope (Figure 4). The other side covered with Dacron mesh appeared infiltrated with pia mater, thus fixing the ABI to the cerebellar aspect of the lateral recess. It was necessary to transect the Dacron mesh from the ABI array and leave the mesh in situ. In stimulated animals, the surface of the CNC appeared brownish coloured (Figure 5).

From a pathological point of view, in all the cases, stimulated or not, where the ABI was successfully placed at the level of the lateral recess of the IV ventricle, only a minor pial thickening was observed in the surface of the brainstem (Figure 6). Neuropathological examination of the cerebellar surface revealed a fusocellular reaction, presence of brown-black granular pigmentation, Dacron filaments, with, and without, giant cell reaction. All these changes are attributed to trauma to the flocculus, produced during its surgical retraction to achieve a better visual control of the lateral recess. In stimulated animals these lesions may also be related with traction forces delivered by the ABI-stimulator, as in implanted animals the ABI is stabilized and attached to the cerebellar flocculus with the Dacron. Nevertheless, the CNC was fairly intact and did not show substantial alterations compared to control animals.

4. Complications – infection

All primates tolerated the surgical procedure well. There was no mortality. During the survival period there were no substantial differences in behaviour or clinical status of animals from group C and D. Within the autopsy procedure of the animal D8, an ulceration of the implantation site was observed. It was a rounded and wet lesion on the surface of the CNC (Figure 7). Pathological examination of the brainstem revealed an intraparenchematous accumulation of polymorphonuclear leukocytes, consistent with an abscess (Figure 8), and ample destruction of the CNC area.

Discussion

To our knowledge this is the first paper in the literature concerning chronic surface electrostimulation of the cochlear nuclei in primates. There are a few papers reporting on surface or deep stimulation, but animal models were usually non-primate species, and stimulation was performed in an acute model.[4,5] Given the scarce pathological information available in humans,[6] the relevance of our paper is that we present a primate model with a chronic surface stimulation, that represents the most equivalent experimental situation to that in human ABI-patients.

As a result of our investigation we can conclude that there are several issues that play a major role in the outcome of implanted animals. One of the most important issues is the surgical ability to place the ABI without trauma, in an extraparenchemal location. The same surgical landmarks that are used in humans[7] are advisable for the location of the CNC in an experimental primate implantation. Also, the traction forces of the ABI may also provoke a tendency to the mobilization or extrusion of the device. As a result of the external connection of the device, ascending infection of the cerebellopontine angle may occur, as it did in animal D8, and was previously reported in humans by Terr *et al.*[6]

The presence of the surface ABI, regardless of its activation, did not induce significant changes in the morphological observations in the CNC, although these will be the subject of further investigation by immunostaining methods. In optimum conditions, the absence of significant damage in the cerebellopontine angle, and the possibility of removing the ABI causing no additional lesions, permit us to think that re-implantation procedures may be attempted if needed.

Conclusions

The total or partial destruction of the CNC observed in the first four cases of group C should be attributed to surgical damage. It is crucial to have a good command of the CNC topography to implant the ABI properly. The materials used for the ABI

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(silicone, Dacron, and platinum) are suitable for implantation on the CNC of the brainstem and have an adequate biotolerance. The presence of a thin capsule around the side of the ABI containing the platinum electrodes suggests that it may be possible to perform explantation surgery without producing relevant damage to the brainstem. Finally, the use of an ABI connected externally to a stimulator may facilitate infection and increase the possibility of ABI displacement.

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