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Case report
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Neurofibromatosis type 2: case report

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ABSTRACT

Aim. *The paper presents the world's first ever case of neurofibromatosis type 2 treated with bilateral resection of vestibular schwannomas and sequential implantation of auditory brainstem implants (ABI) stimulating the brainstem auditory nuclei.*

Case. *The 30-year-old male patient at the age of 26 presented with clinical symptoms of neurofibromatosis type 2 and underwent bilateral resection of schwannoma with sequential implantantion of auditory brainstem implants. Moreover, he had also a subtotal resection of intraspinal, sacral and retroperitoneal schwannomas. His bilateral pareisi of lower limbs has receded completely.*

Comment. *The management of patients with neurofibromatosis type 2 requires a multidisciplinary approach and co-operation of specialists from different disciplines.*

Key words: neurofibromatosis type 2 / schwannoma / auditory brainstem implants / ABI

The authors present a male patient (aged 30) with clinical symptoms of neurofibromatosis type 2, being the first ever case in which a sequential resection of lesions situated within auditory nerves was followed by bilateral implantation of auditory brainstem implants [1]. Neurocutaneous syndromes (phakomatosis) are innate or inherited disorders resulting in lesions both of the skin and of the central nervous system. These disorders may be inherited or sporadic [2]. Phakomatosis may take the following forms: tuberous sclerosis, neurofibromatosis, the Ehlers-Danlos syndrome, *pseudoxanthoma elasticum*, the Rendu–Osler–Weber syndrome, Fabry's disease, the Sturge-Weber syndrome, progressive facial hemiatrophy, ataxia-telangiectasia, kinky hair syndrome, cerebrotendineous xanthomatosis, epidermal nevous syndrome, hypomelanosis of Ito, neurocutaneous melanosis, von Hippel-Lindau disease, Wyburn-Mason syndrome, and xeroderma pigmentosum [2, 3, 4].

Neurofibromatosis is a genetic disorder characterized by neurocutaneous changes. Two types of neurofibromatosis are distinguished: type 1 (NF1) and type 2 (NF2). Some authors distinguish also segmental neurofibromatosis (NF3) and familial *café au lait* spots (NF4) [3]. NF1 is the most common among neurocutaneous syndromes, with the incidence rate of 1 per 3.000-3.500 births, while the rate for NF2 is 1 per 50.000 births. About 50% NF1 and 10% NF2 cases are caused by a spontaneous mutation [2, 5]. Diagnostic criteria for type 1 and type 2 neurofibromatosis are shown in Table 1 [2, 6].

Table 1. *Diagnostic criteria for neurofibromatosis type 1 and type 2 [2, 6]*

Diagnostic criteria for neurofibromatosis type 1 **Two or more of the following:**
1. Six or more *café-au-lait* spots 15 mm or larger in post-pubertal individuals, 5 mm or larger in pre-pubertal individuals;
2. Freckling in the axilla or groin;
3. Optic glioma (tumor of the optic pathway);
4. Two or more neurofibromas or one or more plexiform neurofibroma;
5. A first-degree relative with NF1;
6. Two or more Lisch nodules (benign iris hamartomas);
7. A distinctive bony lesion (dysplasia of the sphenoid bone or thinning of long bone cortex with or without pseudarthrosis).
Diagnostic criteria for neurofibromatosis type 2:
1. Bilateral vestibular schwannomas (or acoustic neuromas) of nerve VIII, confirmed by MRI, CT or histological examination);
2. A first-degree relative with NF2 and unilateral tumor of nerve VIII;
3. A first-degree relative with NF2 and any two of the following tumor types: neurofibroma, meningioma, schwannoma, glioma, or juvenile posterior subcapsular lenticular opacity.

Neurofibromatosis type 1 (von Reclinghausen's disease) was first documented by von Reclinghausen in 1882. This innate syndrome of neurocutaneous conditions is an autosomal dominant genetic disorder caused by a mutation affecting exon 60 of the NF1 gene located on the long arm (q) of chromosome 17. Neurofibromin, the NF1 gene product, is partially homologous with a GPTase-activating protein. About 100 mutations in this gene have been identified [2, 5, 7, 8]. Manifestations of neurofibromatosis type 1 include several categories: *cutaneous symptoms (skin conditions) – café au lait* spots, subcutaneous neurofibromas, plexiform neurofibromas, freckles in the armpit; *systemic symptoms* – Lisch nodules (pigmented iris hamartomas), renal artery dysplasia, adrenal chromocytoma, dysplasia of cerebral vessels – Moyamoya disease; *neurological symptoms* – optic nerve glioma, optic nerve atrophy with progressive loss of vision, sometimes pain or exophtalmos, ependymomas, meningiomas, astrocytomas, neurofibromas and neurinomas (schwannomas) [2, 5, 7]. Von Reclinghausen's disease is incurable and the patient should be under continuous medical surveillance, especially that neoplastic changes are frequently associated with this disease [9, 10, 11].

*Neurofibromatosis type 2 (*NF2, central NF) is an autosomal dominant genetic disorder, with spontaneous mutation in 10% of cases. Mutations affect the NF2 gene located on the 22 q11-13.1. chromosome. The NF2 gene product called schwannomin or merlin (595 amino acids) is responsible for suppression of neoplasm formation, and a dysfunction of the NF2 gene contributes to the frequent occurrence of CNS tumors in patients with NF2. In this condition severity of the clinical course is related to the nature of the gene mutation [2].

NF2 symptoms include bilateral vestibular schwannomas (or acoustic neuromas) together with the resulting progressive retrocochlear hearing loss, tinnitus, vertigo and headaches. In advanced stages of the condition facial nerve paralysis may occur. The onset of these symptoms is in adolescence or early adulthood. Other possible disorders include acoustic nerve tumors and comorbid CNS tumors in various sites within the brain and spinal cord (e.g. meningiomas, ependymomas, astrocytomas). Sometimes schwannomas of other cranial nerves can be seen, e.g. trigeminal (5^{th}) or facial (7^{th}) nerve neuromas, as well as ocular conditions: cataracts, opacification of the lens, etc. Skin changes presenting as spots similar to these occurring in NF1, but less numerous and smaller, may be totally absent! Typically no Lisch nodules are observed. Subcutaneous neurofibromas are much less common [2]. In neurofibromatosis type 2 the following prevalence rates of particular conditions are reported: acoustic neuroma in 90%, neurofibroma of the skin 90%, neurofibromas of the cranial nerves and meningiomas 50%, neuromas of spinal nerves and of peripheral nerve stems 40%, and ependymomas in 20% of cases [2, 11, 12].

NF1 and NF2 do not occur in different members of the same family, since these conditions are caused by mutations in different genes [2].

Neurofibromas, benign tumors arising from peripheral nerves, consist mostly of Schwann cells and fibroblasts, but they contain also intraepithelial pericytes and mast cells [9, 10, 13, 14]. They may develop at any age, increasing in size and number after puberty. Plexiform schwannomas often develop on the face and may cause considerable deformations. The lifetime risk of their malignant transformation is 5 percent [9, 10, 13, 14] (Fig. 4).

The diagnostics of neurofibromatosis type 2 include clinical symptom assessment, family interview, histopathological examination, radiological assessment, genetic counseling to establish NF2 incidence among first-degree relatives, prenatal testing. NF2 symptoms emerge and are diagnosed at the age of 20 on the average. Neurofibromatosis type 2 is an incurable condition [2, 4].

The return to the world of sound can be accomplished due to effective stimulation of auditory nuclei using a brainstem implant. Its construction is similar to that of the cochlear implant, except for a different tip of the electrode stimulating brainstem auditory nuclei. Surgical implantation of cochlear implants was initiated in Poland by Skarżyński in 1992 [15], while the first brainstem implant in Poland was constructed by an international team under his direction in 1998 [16].

The first ever patient was implanted with a brainstem implant at the Los Angeles-based House Ear Institute, USA, in 1997 [16]. At present several types of brainstem implants stimulating auditory nuclei are available, differing in the number of channels in the active electrode. The surgery typically includes acoustic neuroma resection followed by implantation of a brainstem implant (ABI) [17].

It should be noted that under physiological conditions the proper auditory receptors are the hair cells in the cochlear part of the inner ear. Excitation of the hair cells in the cochlea produces micro-impulses transmitted via auditory nerves to the ventral and dorsal auditory nuclei in the brainstem. From there via the crossing auditory pathways they reach the auditory centers in the cerebral cortex, where they are processed as meaningful auditory information [17, 18].

CASE REPORT

The patient's first symptom noted at age 5 by his parents was a "subcutaneous nodule" located on the back. At age 12-13 the patient underwent 7 surgeries to remove his subcutaneous tumors subsequently diagnosed as neurofibromas in histopathological examination. At age 24 he was hospitalized for the first time at the Laryngology Ward of the Bielański Hospital for a sudden onset of vertigo, balance disorders and vomiting. In a medical examination the patient was diagnosed with nystagmus with no hearing disorders. A head MRI scan revealed tumors situated bilaterally in the cerebellopontine angle. On the grounds of the patient's medical history interview, his symptoms, and the brain MRI findings he was diagnosed with neurofibromatosis type 2. Neither his parents nor sister and other family members had ever suffered from a similar condition.

Following comprehensive diagnostic procedures performed at the Institute of Physiology and Pathology of Hearing with view not only to the tumor resection, but also to simultaneous implantation of an acoustic brainstem implant (ABI), the patient was qualified for surgery. He underwent the surgery on Feb. 9th, 2006 at the Neurosurgery Clinic in Fulda, Germany, under the terms of a scientific collaboration program. A cerebropontine angle (CPA) tumor compressing the brainstem and causing practically a total hearing loss in the right ear was removed. During the same surgery an ABI implant was implanted to stimulate the ipsilateral brainstem auditory nuclei. The implant was activated and the patient was provided with further rehabilitation and care under supervision of a number of specialists – physicians, clinical engineers, psychologists, speech therapists, teachers and technicians at the Department of Implants and Auditory Perception of the Institute of Physiology and Pathology of Hearing. The patient used his right-sided ABI implant together with a hearing aid placed in his left ear in which he had some residual hearing preserved. Two years later a contralateral surgery was performed since the patient had lost his residual hearing and his left-sided neurofibroma had increased in size over this period. On March 28th, 2008 he underwent a surgical removal of a giant cochlear neurofibroma on the left side, with a simultaneous implantation of an ipsilateral ABI implant at the Otorhinolaryngology Surgical Clinic of the Institute of Physiology and Pathology of Hearing in Kajetany. The surgery was complicated by a posterior fossa hematoma in the left cerebellar hemisphere. On March 29th, 2008 the patient was reoperated, the hematoma was removed with an intraoperative monitoring of the auditory nuclei stimulation (Fig. 1 and 2). Both the postoperative course and the prior activation of the right-sided ABI implant were uneventful, in collaboration with the same multidisciplinary team of specialists. The levels of sound identification, including speech comprehension, attained by the patient were satisfactory. At that time the patient was the first ever person bilaterally implanted with auditory brainstem implants [1].

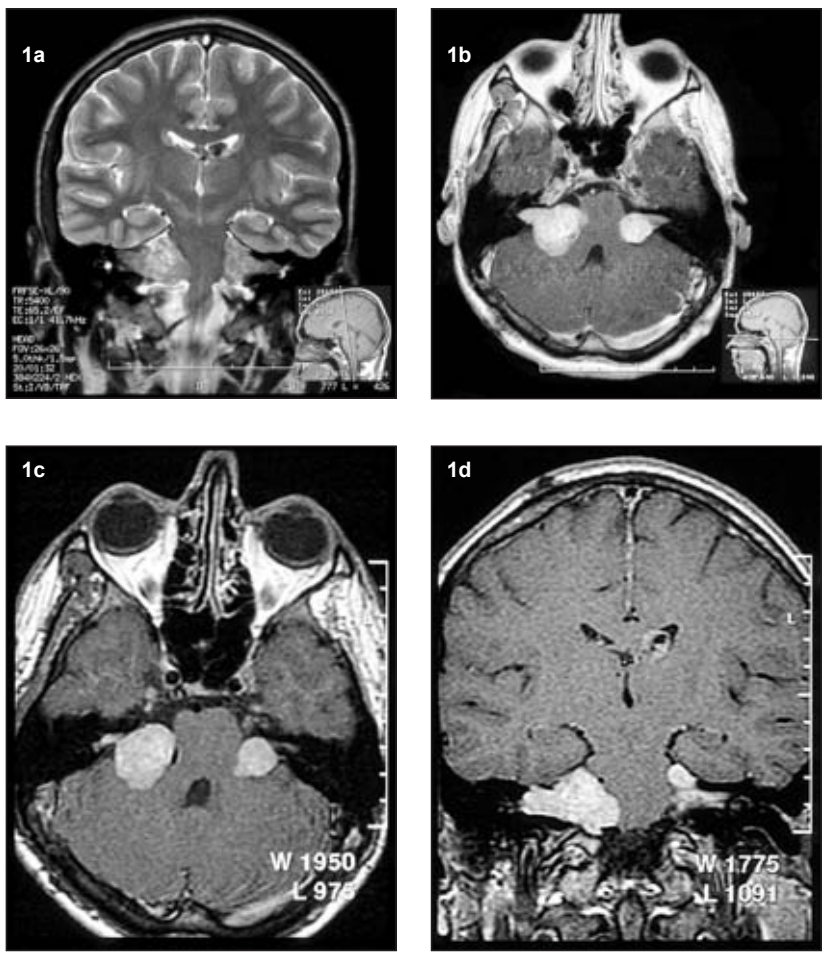

***Figure 1a-d**. MRI brain scans showing bilateral schwannomas of the 8th nerve*

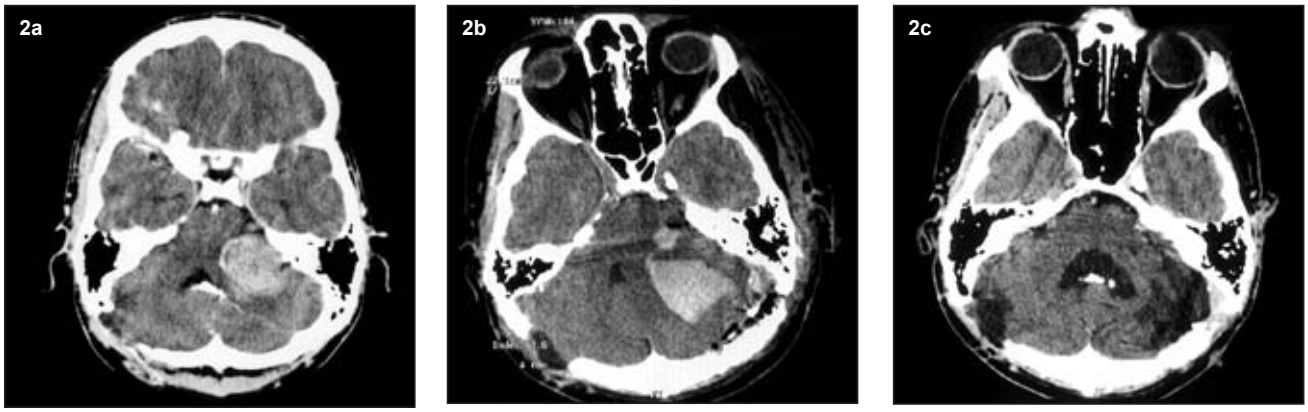

Figure 2. *CT scan of the brain: (a) A giant hemangioma of the vestibular nerve is visible on the left side; (b) A haemorrhagic focus in the left cerebellar hemisphere, shifting the fourth ventricle to the right side; (c) At the 3-month postoperative follow-up a vascular scar after the hemorrhagic focus can be seen*

On Aug. 15th, 2008 the patient experienced sudden pains in the lumbosacral spine with simultaneous bilateral lower limb paresis. Within 10 days he lost his ability to walk and was confined to a wheelchair. He was receiving Dexamethasone, Tramadol, Gabapentine and many analgesics. He was hospitalized at the Neurosurgery Department of the Institute of Psychiatry and Neurology from Aug. 28th to Oct. 10th, 2008. On Sept. 2nd 2008 he underwent a surgery including left-sided sacrotomy, L3, L4 and L5 hemilaminectomy, with resection of a tumor occupying the spinal canal, sacral bone and extraperitoneal space (Fig. 3).

On Sept. 30th 2008 the patient was reoperated: plastic surgery and sealing up of his meningeal sac at the previously operated levels were performed using fibrin sealant (Tissucol) and autogenic fat tissue. A neuropathological examination indicated a nerve sheath tumor (schwannoma) of Antoni A-type mostly (Fig. 4).

On Oct 17th, 2008 the patient was admitted to the Neurological Rehabilitation Unit, Institute of Psychiatry and Neurology, for rehabilitation of his paretic lower limbs. As regards his neurological status on admission, it was found that owing to his auditory brainstem implants the patient had an almost 100% hearing ability (on hearing tests in quiet), and an almost 80% ability of hearing (as assessed by hearing tests in noise). He manifested right-sided Horner's syndrome, soft speech, decreased muscle strength in the lower extremities 1> p (score 4 in the Lovett scale), slightly spastically enhanced muscle tone in the lower limbs, absent knee and ankle jerks, difficulty with dorsiflexion and ventriflexion of feet, unsteadiness on Romberg's test, a wide-base gait while using a walking frame, with assistance. The patient was incapable of heel and toe walking. His skin abnormalities included *café au lait* spots, as well as postoperative scars after subcutaneous nodules surgery and ABIs implantation. On the patient's discharge home after the 3-week rehabilitation he had considerably improved muscle strength in his lower limbs and was able to walk independently. At a 4-year follow-up no evident lower limb paresis was found. A few weeks earlier the patient had participated in one of the Warsaw marathons, a 10-km run, and reached the finish line among mid-level runners.

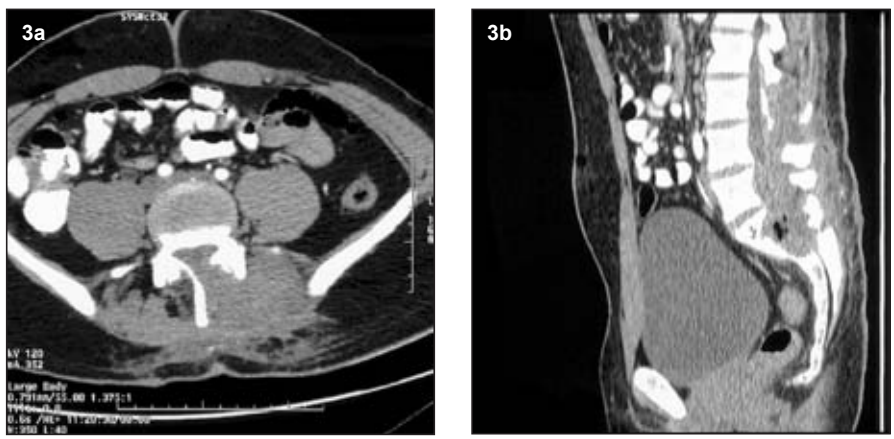

Figure 3. *Lumbosacral spine CT scans showing: (a) cross-section; (b) sagittal section – a huge abnormal mass involving the sacrum, spinal canal and the lesser (minor) pelvis*

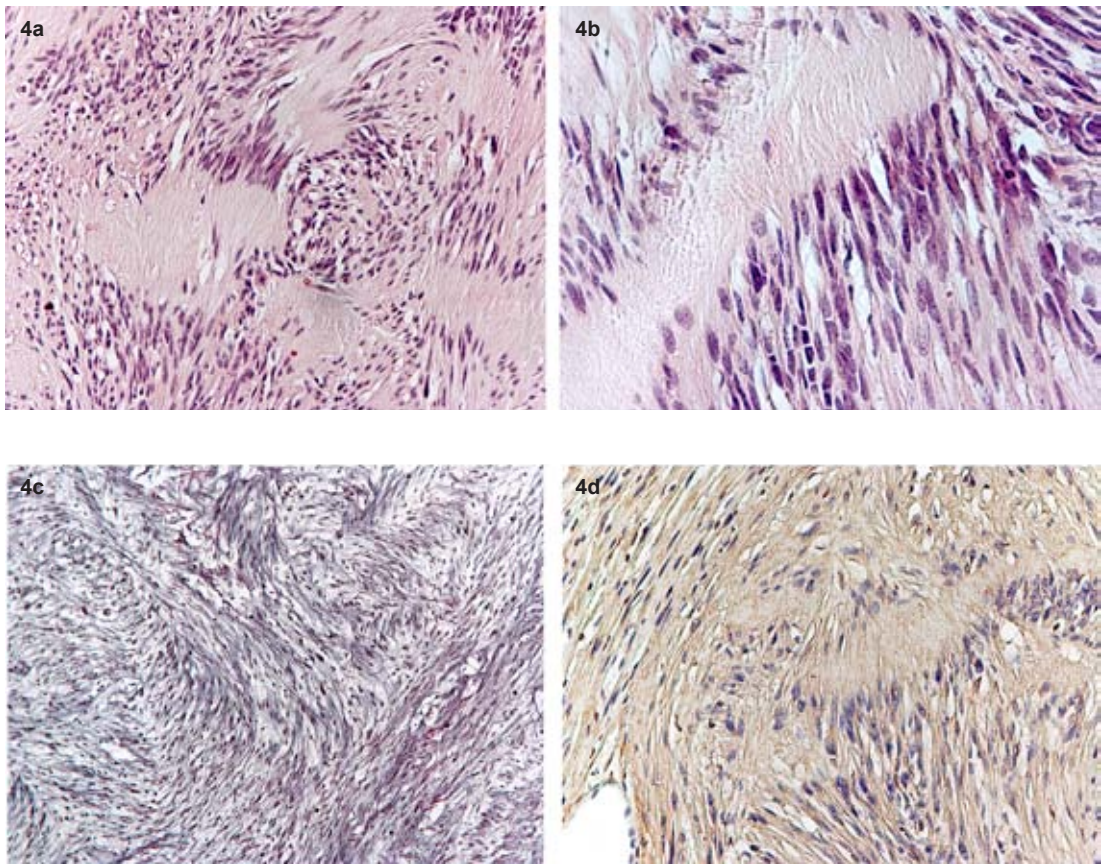

Figure 4. *(a) Acoustic neuroma (schwannoma) composed of spindle cells arranged in strands. HEx200; (b) Parallel palisades of spindle-shaped cells with slender, chromatin-rich nuclei. HEx400; (c) Dispersed reticular fibres in the Antoni type A schwannoma. Gomori x100.; (D) A positive staining reaction with anti-Vimentin antibodies in neoplastic cells of the schwannoma. Vimentin x200*

It should be noted that the patient leads a very busy life as a professional. Moreover, he is a member of a musical ensemble. His hearing abilities enabled him to record his third album. The first one had been recorded prior to the surgical removal of his brainstem changes, and the second album – after the surgery of his right-sided tumor and his first ABI implantation. Using both his ABIs he has participated in a national song competition and in a number of scientific conferences. Among other ones, he took part in the 9th European Conference on Auditory Implants held in Warsaw in May 2009, where he presented in English his experiences as an implanted patient.

DISUCSSION

We presented a case of the first ever patient after sequential removal of changes affecting auditory nerves, with implantation of bilateral brainstem auditory implants [1]. Not only the bilateral implantation seems to be noteworthy, but also the accomplished quality of the patient's new hearing abilities so useful in his life activities. Moreover, thecase exemplifies safety of a long-term bilateral electrical stimulation of the brainstem (while the brainstem surface had been considerably deformed by extensive pathological changes). The auditory outcomes accomplished in this case were confirmed by an independent scientific research team headed by Professor B. Shannon from Los Angeles, the pioneer of the ABI implantation program, and have greatly contributed to the program development and popularization in the contemporary science and medicine [19, 20]. Differently situated pathological changes seen and effectively treated in subsequent cases demonstrate that multidisciplinary care provided to this group of patients yields satisfactory therapeutic outcomes.

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