Table 3 Patients who have at least one pathogenic mutation identified in this study

Patient	DNA level	Protein level	Clinical diagnosis	OAE	Age at diagnosis	Hearing loss level
1	c.1422T>A / c.5567G>A	p.Y474X / p.R1856Q	ANSD	+	1y6m	Profound
2	c.1422T>A / c.5816G>A	p.Y474X / p.R1939Q	ANSD	+	NA	Profound
3	c.5816G>A / c.5816G>A	p.R1939Q / p.R1939Q	ANSD	+	4m	Profound
4	c.5816G>A / c.5816G>A	p.R1939Q / p.R1939Q	ANSD	+	10m	Profound
5	c.5816G>A / c.5816G>A	p.R1939Q / p.R1939Q	ANSD	+	NA	Profound
6	c.4748G>A / c.5816G>A	p.R1583H / p.R1939Q	NSHL	NA	6m	Profound
7	c.2151G>A / c.5816G>A	p.W717X / p.R1939Q	NSHL	-	1y4m	Profound
8	c.5816G>A / -	p.R1939Q /-	ANSD	+	1y5m	Profound
9	c.5816G>A / -	p.R1939Q /-	ANSD	+	7m	Profound
10	c.1194T>A / -	p.D398E / -	NSHL	NA	NA	Profound
11	c.1350C>G / -	p.D450E / -	NSHL	NA	2y	Severe
12	c.2180A>G / -	p.N727S / -	NSHL	NA	6m	Profound
13	c.2180A>G / -	p.N727S / -	NSHL	NA	1y	Severe
14	c.4103C>G / -	p.S1368X / -	NSHL	NA	7m	Profound
15	c.5332G>A / -	p.V1778I / -	NSHL	NA	NA	Profound
16	c.5408A>C / -	p.E1803A / -	NSHL	NA	4m	Profound

ANSD Auditory neuropathy spectrum disorder, *NSHL* Nonsyndromic sensorineural hearing loss.

As seen in previous mutation screening reports, including those for *OTOF* [12,23,30], there were a significant number of heterozygous cases without a second mutation even after direct sequencing of the coding region of the gene. Possible explanations are: 1) the existence of a second mutation in the intron or regulatory region of *OTOF*, which has not been explored, 2) the existence of a large deletion [31], 3) contribution to hearing loss by an additional modulatory gene, and 4) the existence of a mutation in another gene and just coincidental carrying of the *OTOF* mutation.

As seen in Table 3, two heterozygous patients (#8, 9) having the ANSD phenotype, are most likely to have *OTOF* related deafness.

It is assumed that *OTOF* mutations accounted for deafness in at least 7, and possibly 16, of the 160 patients (4.4-10.0%). As described in the subject section, we excluded the subjects carrying *GJB2* and *SLC26A4* mutations. We also excluded another responsible gene (*PJVK*), because no mutations in this gene were found. Since the frequencies of *GJB2* and *SLC26A4* gene mutations among the patients with nonsyndromic severe to profound congenital SNHL are 27.0% based on our database, mutation frequency of *OTOF* among the total of severe to profound recessive nonsyndromic SNHL is considered to be about 3.2-7.3% (which is calculated by ((7-16)/160×(100/73))×100%). Although simple comparison regarding frequency is difficult because of sampling bias, it is estimated that the frequency of OTOF mutations in Japanese may be almost equal to other populations, as mutation frequency of OTOF was reported at 2.3% (13/557) in Pakistanis [11], 5.0% in Turkish [32], 1.4% (1/73) in Chinese [23], and 18.2% (4/22) in Taiwanese [29], and 3.2% (23/708) in Spanish [12]. Although simple comparison regarding frequency is difficult because of sampling bias, it is estimated that the frequency of *OTOF* mutations in Japanese may be almost equal to other populations. In Japanese, *GJB2, SLC26A4, CDH23* and the 1555A>G mutation in the mitochondrial 12S rRNA are the major causes of hearing loss [33]. Considering the frequency, the *OTOF* gene may be one of the candidate genes to be screened for recessive severe to profound recessive SNHL.

The benefits of cochlear implantation for patients with ANSD has varied [34,35], but implantation has been shown to be effective for the patients with *OTOF* mutations [15,16,36], because their auditory nerves and spiral ganglions are preserved. Consequently, if an *OTOF* mutation is identified in a deaf patient, we can anticipate a good outcome of cochlear implantation, therefore, it is important and meaningful to identify genetic mutations in patients.

Most patients with *OTOF* mutations have a phenotype of stable prelingual and severe to profound nonsyndromic hearing loss. On the other hand, other phenotypes have also been reported. For example, a Taiwanese patient with an p.E1700Q mutation displayed moderate to profound progressive hearing loss [29]. Temperature sensitive ANSD, a particular form of ANSD, has also been reported in some populations [10,23,37].

In the very young child, electrophysiological testing may indicate that *OTOF*-related deafness is ANSD, but

by age two OAEs have generally disappeared and the test results are more in accord with the findings of cochlear lesions [14]. Therefore, if OAE is not tested at a very early age, patients with *OTOF* mutations are not deemed to have ANSD (i.e., hidden ANSD). In fact, 9 out of our 16 patients were diagnosed genetically as nonsyndromic sensorineural hearing loss (NSHL). According to the present data, screening for *OTOF* is necessary not only for the patients diagnosed with ANSD, but also should be extended to ARNSHL cases. The current data indicated that OAE testing must always be conducted in addition to ABR in infants. And we should bear in mind that there may be patients with *OTOF* mutations among the patients diagnosed as having ARNSHL.

Conclusions

The present study showed that *OTOF* mutations accounted for 3.2-7.3% of recessive severe to profound SNHL patients in Japan. *OTOF* mutations are a frequent cause in the Japanese deafness population and mutation screening should be considered regardless of the presence/absence of OAEs.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YI and SN carried out the molecular genetic studies and the sequence alignment, and participated in drafting the manuscript. SU conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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References

1. Starr A, Picton TW, Sininger Y, Hood LJ, Berlin CI: Auditory neuropathy. *Brain* 1996, 119(Pt 3):741–753.
2. Kaga K, Nakamura M, Shinogami M, Tsuzuku T, Yamada K, Shindo M: Auditory nerve disease of both ears revealed by auditory brainstem responses, electrocochleography and otoacoustic emissions. *Scand Audiol* 1996, 25(4):233–238.
3. Berlin CI, Hood L, Morlet T, Rose K, Brashears S: Auditory neuropathy/dys-synchrony: diagnosis and management. *Ment Retard Dev Disabil Res Rev* 2003, 9(4):225–231.
4. Roush P, Frymark T, Venediktov R, Wang B: Audiological Management of Auditory Neuropathy Spectrum Disorder in Children: A Systematic Review of the Literature. *Am J Audiol* 2011, (20):159–170.
5. Madden C, Rutter M, Hilbert L, Greinwald JH Jr, Choo DI: Clinical and audiological features in auditory neuropathy. *Arch Otolaryngol Head Neck Surg* 2002, 128(9):1026–1030.
6. Starr A, Sininger YS, Pratt H: The varieties of auditory neuropathy. *J Basic Clin Physiol Pharmacol* 2000, 11(3):215–230.
7. Manchaiah VK, Zhao F, Danesh AA, Duprey R: The genetic basis of auditory neuropathy spectrum disorder (ANSD). *Int J Pediatr Otorhinolaryngol* 2011, 75(2):151–158.
8. Roux I, Safieddine S, Nouvian R, Grati M, Simmler MC, Bahloul A, Perfettini I, Le Gall M, Rostaing P, Hamard G, *et al*: Otoferlin, defective in a human deafness form, is essential for exocytosis at the auditory ribbon synapse. *Cell* 2006, 127(2):277–289.
9. Yasunaga S, Grati M, Chardenoux S, Smith TN, Friedman TB, Lalwani AK, Wilcox ER, Petit C: OTOF encodes multiple long and short isoforms: genetic evidence that the long ones underlie recessive deafness DFNB9. *Am J Hum Genet* 2000, 67(3):591–600.
10. Varga R, Avenarius MR, Kelley PM, Keats BJ, Berlin CI, Hood LJ, Morlet TG, Brashears SM, Starr A, Cohn ES, *et al*: OTOF mutations revealed by genetic analysis of hearing loss families including a potential temperature sensitive auditory neuropathy allele. *J Med Genet* 2006, 43(7):576–581.
11. Choi BY, Ahmed ZM, Riazuddin S, Bhinder MA, Shahzad M, Husnain T, Griffith AJ, Friedman TB: Identities and frequencies of mutations of the otoferlin gene (OTOF) causing DFNB9 deafness in Pakistan. *Clin Genet* 2009, 75(3):237–243.
12. Rodriguez-Ballesteros M, Reynoso R, Olarte M, Villamar M, Morera C, Santarelli R, Arslan E, Meda C, Curet C, Volter C, *et al*: A multicenter study on the prevalence and spectrum of mutations in the otoferlin gene (OTOF) in subjects with nonsyndromic hearing impairment and auditory neuropathy. *Hum Mutat* 2008, 29(6):823–831.
13. Matsunaga T, Mutai H, Kunishima S, Namba K, Morimoto N, Shinjo Y, Arimoto Y, Kataoka Y, Shintani T, Morita N, *et al*: A prevalent founder mutation and genotype-phenotype correlations of OTOF in Japanese patients with auditory neuropathy. *Clin Genet* 2012, 82(5):425–432.
14. Smith RJH, Gurrola JG, Kelley PM: OTOF-Related Deafness. In *GeneReviews [Internet]*. Edited by Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K. Seattle, WA: University of Washington; 2008. updated 2011.
15. Rouillon I, Marcolla A, Roux I, Marlin S, Feldmann D, Couderc R, Jonard L, Petit C, Denoyelle F, Garabedian EN, *et al*: Results of cochlear implantation in two children with mutations in the OTOF gene. *Int J Pediatr Otorhinolaryngol* 2006, 70(4):689–696
16. Wu CC, Liu TC, Wang SH, Hsu CJ, Wu CM: Genetic characteristics in children with cochlear implants and the corresponding auditory performance. *Laryngoscope* 2011, 121(6):1287–1293.
17. Hilgert N, Smith RJ, Van Camp G: Forty-six genes causing nonsyndromic hearing impairment: which ones should be analyzed in DNA diagnostics? *Mutat Res* 2009, 681(2–3):189–196.
18. Wang K, Li M, Hakonarson H: ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. *Nucleic Acids Res* 2010, 38(16):e164.
19. Liu X, Jian X, Boerwinkle E: dbNSFP: a lightweight database of human nonsynonymous SNPs and their functional predictions. *Hum Mutat* 2011, 32(8):894–899.
20. Chang X, Wang K: wANNOVAR: annotating genetic variants for personal genomes via the web. *J Med Genet* 2012, 49(7):433–436.
21. Wang J, Fan YY, Wang SJ, Liang PF, Wang JL, Qiu JH: Variants of OTOF and PJVK genes in Chinese patients with auditory neuropathy spectrum disorder. *PLoS One* 2011, 6(9):e24000.
22. Varga R, Kelley PM, Keats BJ, Starr A, Leal SM, Cohn E, Kimberling WJ: Non-syndromic recessive auditory neuropathy is the result of mutations in the otoferlin (OTOF) gene. *J Med Genet* 2003, 40(1):45–50.
23. Wang DY, Wang YC, Weil D, Zhao YL, Rao SQ, Zong L, Ji YB, Liu Q, Li JQ, Yang HM, *et al*: Screening mutations of OTOF gene in Chinese patients with auditory neuropathy, including a familial case of temperature-sensitive auditory neuropathy. *BMC Med Genet* 2010, 11:79.
24. Migliosi V, Modamio-Hoybjor S, Moreno-Pelayo MA, Rodriguez-Ballesteros M, Villamar M, Tellería D, Menendez I, Moreno F, Del Castillo I: Q829X, a novel

mutation in the gene encoding otoferlin (OTOF), is frequently found in Spanish patients with prelingual non-syndromic hearing loss. *J Med Genet* 2002, **39**(7):502–506.
25. Mahdieh N, Shirkavand A, Rabbani B, Tekin M, Akbari B, Akbari MT, Zeinali S: Screening of OTOF mutations in Iran: a novel mutation and review. *Int J Pediatr Otorhinolaryngol* 2012, **76**(11):1610–1615.
26. Ohtsuka A, Yuge I, Kimura S, Namba A, Abe S, Van Laer L, Van Camp G, Usami S: GJB2 deafness gene shows a specific spectrum of mutations in Japan, including a frequent founder mutation. *Hum Genet* 2003, 112(4):329–333.
27. Tsukamoto K, Suzuki H, Harada D, Namba A, Abe S, Usami S: Distribution and frequencies of PDS (SLC26A4) mutations in Pendred syndrome and nonsyndromic hearing loss associated with enlarged vestibular aqueduct: a unique spectrum of mutations in Japanese. *Eur J Hum Genet* 2003, 11(12):916–922.
28. Wagatsuma M, Kitoh R, Suzuki H, Fukuoka H, Takumi Y, Usami S: Distribution and frequencies of CDH23 mutations in Japanese patients with non-syndromic hearing loss. *Clin Genet* 2007, **72**(4):339–344.
29. Chiu YH, Wu CC, Lu YC, Chen PJ, Lee WY, Liu AY, Hsu CJ: Mutations in the OTOF gene in Taiwanese patients with auditory neuropathy. *Audiol Neurootol* 2010, 15(6):364–374.
30. Romanos J, Kimura L, Favero ML, Izarra FA, de Mello Auricchio MT, Batissoco AC, Lezirovitz K, Abreu-Silva RS, Mingroni-Netto RC: Novel OTOF mutations in Brazilian patients with auditory neuropathy. *J Hum Genet* 2009, 54(7):382–385.
31. Zadro C, Ciorba A, Fabris A, Morgutti M, Trevisi P, Gasparini P, Martini A: Five new OTOF gene mutations and auditory neuropathy. *Int J Pediatr Otorhinolaryngol* 2010, **74**(5):494–498.
32. Duman D, Sirmaci A, Cengiz FB, Ozdag H, Tekin M: Screening of 38 genes identifies mutations in 62% of families with nonsyndromic deafness in Turkey. *Genet Test Mol Biomarkers* 2011, **15**(1–2):29–33.
33. Usami SI, Nishio SY, Nagano M, Abe S, Yamaguchi T: Simultaneous screening of multiple mutations by invader assay improves molecular diagnosis of hereditary hearing loss: a multicenter study. *PLoS One* 2012, 7(2):e31276.
34. Gibson WP, Sanli H: Auditory neuropathy: an update. *Ear Hear* 2007, 28(2 Suppl):102S–106S.
35. Rance G, Barker EJ: Speech perception in children with auditory neuropathy/dyssynchrony managed with either hearing AIDS or cochlear implants. *Otol Neurotol* 2008, **29**(2):179–182.
36. Rodriguez-Ballesteros M, del Castillo FJ, Martin Y, Moreno-Pelayo MA, Morera C, Prieto F, Marco J, Morant A, Gallo-Teran J, Morales-Angulo C, *et al*: Auditory neuropathy in patients carrying mutations in the otoferlin gene (OTOF). *Hum Mutat* 2003, **22**(6):451–456.
37. Starr A, Sininger Y, Winter M, Derebery MJ, Oba S, Michalewski HJ: Transient deafness due to temperature-sensitive auditory neuropathy. *Ear Hear* 1998, 19(3):169–179.

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Original Paper

Auditory Brainstem Implantation Improves Speech Recognition in Neurofibromatosis Type II Patients

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Key Words
Acoustic neuroma · Auditory brainstem implant · Nonauditory side effects · Open-set sentence recognition · Subjective benefits · Vestibular schwannoma

Abstract
This prospective study aimed to determine speech understanding in neurofibromatosis type II (NF2) patients following implantation of a MED-EL COMBI 40+ auditory brainstem implant (ABI). Patients (n = 32) were enrolled postsurgically. Nonauditory side effects were evaluated at fitting and audiological performance was determined using the Sound Effects Recognition Test (SERT), Monosyllable-Trochee-Polysyllable (MTP) test and open-set sentence tests. Subjective benefits were determined by questionnaire. ABI activation was documented in 27 patients, 2 patients were too ill for testing and 3 patients were without any auditory perception. SERT and MTP outcomes under auditory-only conditions improved significantly between first fitting and 12-month follow-up. Open-set sentence recognition improved from 5% at first fitting to 37% after 12 months. The number of active electrodes had no significant effect on performance. All questionnaire respondents were 'satisfied' to 'very satisfied' with their ABI. An ABI is an effective treatment option in NF2 patients with the potential to provide open-set speech recognition and subjective benefits. To our knowledge, the data presented herein is exceptional in terms of the open-set speech perception achieved in NF2 patients.

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Introduction

Neurofibromatosis type II (NF2) typically leads to a clinical picture dominated by neurological symptoms caused by the development of multiple benign spinal and brain tumors (Schwann cell tumors) [1]. The hallmark of NF2 is the development of bilateral vestibular schwannomas. However, unilateral vestibular schwannomas, a family history of NF2, or any two of meningioma, glioma, neurofibroma, schwannoma or posterior subcapsular opacities are also diagnostic criteria for NF2 [2].

Vestibular schwannomas involve the internal auditory canal or cerebellopontine angle and frequently result in severe disability and reduced life expectancy. Complete loss of hearing is common in the majority of bilaterally affected patients due to the destruction of the auditory nerve, usually resulting either from tumor growth or from treatment (by surgical tumor removal or radiosurgery). After surgical treatment of the tumor the hearing preservation of patients, who showed useful preoperative hearing, ranges from 32 to 88% [3–6]. Patients with deafness and preserved function of the cochlear nerve are good candidates for cochlear implantation [7, 8]. However, in patients with complete hearing loss, following nerve degeneration or nerve loss by tumor destruction, an auditory brainstem implant (ABI) represents the only remaining therapeutic option to provide patients with auditory input [9–13].

Several studies indicate that ABIs are effective and safe in providing useful auditory sensations in most patients with NF2 who would otherwise be totally deaf [9, 14–21]. However, only a minority of the patients in the aforementioned studies achieved open-set speech discrimination and the speech recognition of individuals with an ABI varied considerably; most patients use their ABI to facilitate lip-reading and can only recognize environmental sounds [9, 15–19, 22]. Importantly, even those with strongly limited speech recognition reported being very satisfied with their implant, showing that NF2 patients can gain remarkable objective and subjective benefits from ABI use [18].

Another factor contributing to the performance of an ABI are nonauditory side effects. Typically, nonauditory side effects are produced via inadvertent stimulation of the cerebellar flocculus, the cerebellar peduncle, the long sensory tracts or the facial nerve. It is not unusual for NF2 patients with an ABI to experience nonauditory sensations [23]. Up to 42% of users experience them [24, 25] and almost all of these nonauditory effects are benign, but they cause considerable discomfort to the individual [23]. Nonauditory side effects are usually managed by selecting the configuration of the electrodes [26], i.e. programming out the stimulus. In multichannel ABIs different sites of electrode stimulation can generate different pitch percepts [27]. Therefore, changes in the frequency spectrum of sounds can be coded for by changes in electrode activation [27]. Consequently, deactivation of electrodes due to nonauditory sensations can potentially affect the performance seen in patients fitted with an ABI. Although reports indicate that the number of functional electrodes affects the performance of speech recognition tests [19, 28], opinions regarding the existence of a correlation between the number of active electrodes and patient performance remain divided.

This study aimed to determine speech understanding capabilities over time in NF2 patients following implantation of an ABI. In particular, this paper evaluated open-set speech understanding and subjective benefits in NF2 patients with an ABI, who experience some auditory sensation, over a 1-year postactivation period. In addition, the frequency and consequences of nonauditory side effects were assessed.

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Table 1. Subject demographics

Subject ID	Age at implantation		Gender	Side implanted	Number of active electrodes				
	years	months			first fitting	1 month	3 months	6 months	12 months
1	41	8	M	R	10	10	–	–	–
2	34	11	F	L	10	10	11	10	–
3	42	3	M	R	5	4	5	5	2
4	63	7	M	R	10	9	12	12	12
5	49	10	M	R	12	–	12	12	12
6[1]	42	4	F	L	too sick to test				
7	36	5	M	L	7	8	–	9	9
8	22	7	M	L	7	–	8	8	8
9[1]	48	4	F	R	nonuser				
10	45	12	F	R	12	12	9	8	8
11	23	1	M	R	–	7	7	7	7
12	35	12	M	R	7	7	7	7	7
13	54	1	F	R	12	12	12	12	12
14	27	7	F	L	9	10	–	9	9
15	25	11	F	R	7	7	7	12	12
16	19	3	F	R	8	8	8	8	7
17[1]	40	12	F	R	nonuser				
18	39	12	M	L	12	8	10	10	10
19[1]	40	3	F	L	too sick to test				
20	51	1	F	L	8	8	6	6	6
21[1]	30	2	M	L	nonuser				
22	21	5	F	R	12	12	12	–	–
23	41	9	F	R	7	7	–	–	–
24	66	11	M	R	10	9	9	9	9
25	39	7	M	R	8	8	–	–	–
26	43	4	F	L	6	6	6	6	–
27	42	10	M	bilateral	6	5	5	5	5
28	31	8	M	L	–	–	–	–	–
29	42	2	M	R	–	–	–	–	–
30[2]	33	6	M	R	–	–	–	–	–
31[2]	26	8	M	L	–	7	7	7	7
32	25	7	F	R	8	8	8	8	8

[1] Not included in data analysis. [2] Revision cases.

Materials and Methods

Patients and Inclusion Criteria

Between April 2001 and July 2009, 32 patients who received a MED-EL COMBI 40+ ABI were enrolled postsurgically in this prospective multicenter study; 16 patients were treated at Würzburg (University of Würzburg, Würzburg, Germany), while the remainder were treated at 6 other centers. The mean age at implantation was 38.4 years (range: 19.0–66.1 years). Individual subject data are shown in table 1. For inclusion in this study, subjects were 15 years or older and diagnosed with NF2. All patients gave written informed consent.

All patients were implanted using the surgical procedure as described by Matthies et al. [16] (2000), Behr et al. [18] (2007) and Jackson et al. [22] (2002); 6 participants received the MED-EL COMBI 40+ and 26 the ABI. The ABI is a development of the COMBI 40+ offering an electronic platform, which allows a maximum stimulation rate of 50.760 compared to 18.180 pulses/second, which was possible with the COMBI 40+. Besides the electronics there is no difference between the 2 implants. Both feature a ceramic housing, offer the CIS+ speech-coding strategy [29], and comprise an electrode carrier with 13 (12 stimulation and 1

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reference) platinum contacts partially embedded in a preshaped flat silicone paddle [18, 22]. In addition, the ABI electrode features a polyester mesh to increase the stability of the electrode array on the surface of the cochlear nucleus.

At the time of enrolment all subjects showed acceptable general health and mental stability. However, at follow-up 5 subjects could not be included in the study due to poor health, which prevented them from performing any tests (subjects 6 and 19), or they were excluded because they did not experience any auditory sensation (subjects 9, 17 and 21). Subjects 27 and 30 underwent ABI implantation a number of years earlier without success. Subject 27 was bilaterally implanted as a nonuser in the left ear, and was tested with the active right implant. Subject 26 had prior ABI experience; however, the ABI lost function following tumor regrowth. Likewise, subject 31 had prior ABI experience; however, trauma resulting in an implant defect led to implantation of a new device on the same side.

Device Fitting

All patients were fitted with the TEMPO+ BTE speech processor. In general, initial stimulation took place 6–8 weeks after surgery and was performed during a 3-day inpatient hospitalization. In some cases an extended rehabilitation period after tumor removal was required and led to delayed implant activation.

First fitting was performed in a monitored environment such as an Intensive Care Unit. Pulse oximetry, continuous echocardiography and noninvasive blood pressure were monitored during the fitting process. Emergency resuscitation equipment and drugs were available and an Advanced Cardiac Life Support certified individual was present. Activation commenced with stimulation of individual electrodes. Patients were instructed to report any auditory and nonauditory sensations. Electrodes with clear auditory percept and no or negligible nonauditory side effects were selected for an initial program.

Following 1–2 days of listening experience and refinement of the initial program the first assessment of performance was conducted. Pitch ranking of the selected electrodes was attempted during first fitting; however, in some cases this was only possible at subsequent fitting sessions. After electrodes were balanced in loudness, participants were asked to name the electrodes with the highest and lowest pitches. Successive repetition and reordering led to a tonotopic ranking of the electrodes.

Follow-up assessment took place at 1, 3, 6 and 12 months postactivation. During follow-up, individual electrode stimulation for loudness, pitch and nonauditory side effects, and speech and sound perception were used to optimize the program. The nature and subjective strength of nonauditory side effects determined which electrode contacts were activated in this study. Contacts were either checked repeatedly with regard to nonauditory side effects at follow-up or were in some instances, depending upon the nature of

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Subjective Benefit Assessment

Six months after first fitting all participants were asked to complete a questionnaire specifically designed to assess the subjective impact of the ABI on the users. The questionnaire consisted of 7 questions assessing topics such as the time needed to become accustomed to the ABI, the influence of the ABI on daily life and listening capacity, as well as the subject's overall impression regarding the ABI.

Statistical Analyses

Descriptive statistics were used to report demographic data and baseline device fitting characteristics. Quantitative data are presented as mean, standard deviation and range (minimum and maximum); qualitative data are presented as absolute and relative frequencies. The Kolmogorov-Smirnov test was used to determine data distribution.

The effects between first fitting and 12-month testing for the SERT, the closed-set MTP test and the open-set sentence test were examined using the nonparametric Mann-Whitney U test. To show the benefit over lip-reading added by the ABI, the auditory gain for open-set sentence test results was calculated by subtracting the mean scores obtained under visual-only conditions from those under auditory-visual conditions.

Outcomes of the 7-item subjective questionnaire are presented as absolute and relative frequencies. Missing data were not replaced but treated as 'missing' values. Data of participating study sites were pooled. To prevent a treatment-by-center interaction, each study site followed an agreed protocol. A p value <0.05 was determined as statistically significant. IBM SPSS Statistics 19 (IBM, Armonk, N.Y., USA) was used for all analyses. Graphs were created in Microsoft Office Excel 2010 (http://www.microsoft.com).

Results

Number of Active Electrodes and Nonauditory Side Effects

At first fitting an average of 8.8 ± 2.2 out of 12 available contacts were activated to provide auditory stimuli to the subjects (table 1). None of the 27 subjects included had less than 5 active electrodes. Over time, the number of active electrodes remained essentially stable. Electrode contacts were deactivated due to several reasons: (1) contacts providing no sensation at all; (2) contacts causing unpleasant sound sensation (sound often described as faint, scratchy or persistent); (3) contacts with the same pitch rank (for optimized fitting); (4) contacts with mixed-auditory and nonauditory sensations (if nonauditory sensations were not tolerated by the subject), and (5) contacts with only nonauditory responses.

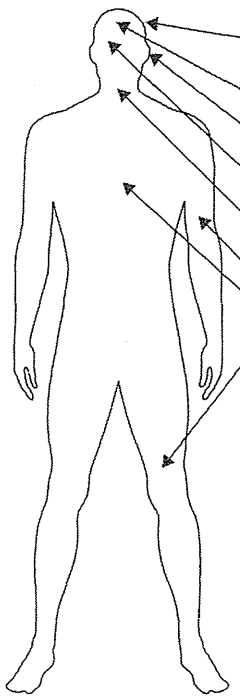
No information was available regarding nonauditory side effects for 7 subjects (25.9%); 8 subjects (29.6%) did not experience any nonauditory side effects. Of the remaining 12 subjects the body location and nonauditory sensation with the number of contacts (deactivated and active) causing the side effect are shown in figure 1. The nature of the side effect(s) led to deactivation in 48 out of 144 total contacts (33.3%); 11 out of 144 contacts (7.6%) were maintained in an active state despite subjects experiencing nonauditory sensations. Amongst these, 2 contacts were deactivated after the first fitting, while 9 were active throughout the duration of the study.

Sound Effect Recognition Test

The SERT was performed by 26 subjects in total. As shown in figure 2, a steady increase in SERT scores averaged across all data available was observed up to the 6-month test interval. The improvement between the first fitting scores and the 12-month test were significant (p = 0.009, n = 11 subjects who performed the test at the first fitting and 12-month test interval).

Monosyllabic-Trochee-Polysyllabic Tests

The closed-set MTP test was performed by 27 subjects in total. The test was scored by correct identification of syllables and words under the auditory-only and auditory-visual



Location	Sensation	Number of contacts deactivated/active		
Head	Headache/knocking, pressure sensation	4	1	
Head	Dizziness	8	1	
Head	Tickling	1		
Temple	Tactile	1	3	
Temple	Pain	1	1	
Ear	Twitching/tickling	2		77.1/72.7%
Eye/eyebrow	Twitching/tickling	2	1	
Eye	Eye movement	4		
Eye	Blurred vision	3		
Chin	Irritation	2	1	
Arm	Unpleasant sensation	2		16.7/18.2%
Chest	Tickling/unpleasant sensation	4	2	
Leg	Twitching	2	1	6.2/9.1%
		48/144	11/144	33.3/7.6%

Fig. 1. Location and frequency of nonauditory sensations experienced by patients with an ABI at first fitting (n = 12).

condition. In both test conditions (auditory-only and auditory-visual) the mean syllable scores reached test ceiling immediately after device activation (data not shown). Individual word scores are shown in table 2.

Under auditory-only conditions the mean correct word score across all data available ('all data' group) was 11.7 ± 6.4 words out of 24 (48.7%) at first fitting. The mean outcome calculated from patients who were tested at all scheduled intervals ('complete' group) was 12.1 ± 6.0 words (50.4%). A steady increase in mean results was observed over the 12-month follow-up period for both the 'all data' and the 'complete' group. The improvement between first fitting scores and 12-month testing was highly significant for auditory-only word recognition (Mann-Whitney U test: $p < 0.001$, $n = 19$).

Under the auditory-visual condition the test ceiling was reached at first fitting. Likewise, no statistically significant difference was observed in the auditory-visual word score between the first fitting and 12-month testing (Mann-Whitney U test: $p = 0.106$, $n = 18$).

Sentence Tests

Sentence tests were performed by 26 subjects in the auditory-visual condition, 23 in the auditory-only condition and 22 in the visual-only condition. Results averaged across all available data under all conditions are shown in figure 3. A highly significant improvement from the first fitting to the 12-month test was observed under the auditory-only (Mann-

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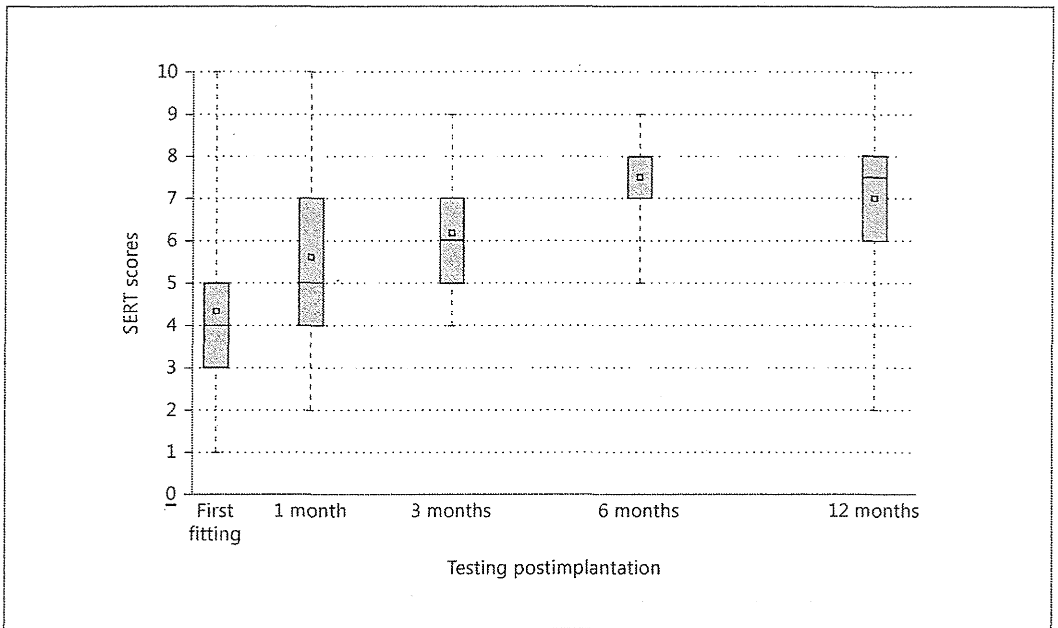

Fig. 2. Environmental sound recognition performance determined by SERT in patients with an ABI after first fitting and 1, 3, 6 and 12 months postactivation. Boxplot whiskers depict sample minimum and maximum; the white square equals the mean value.

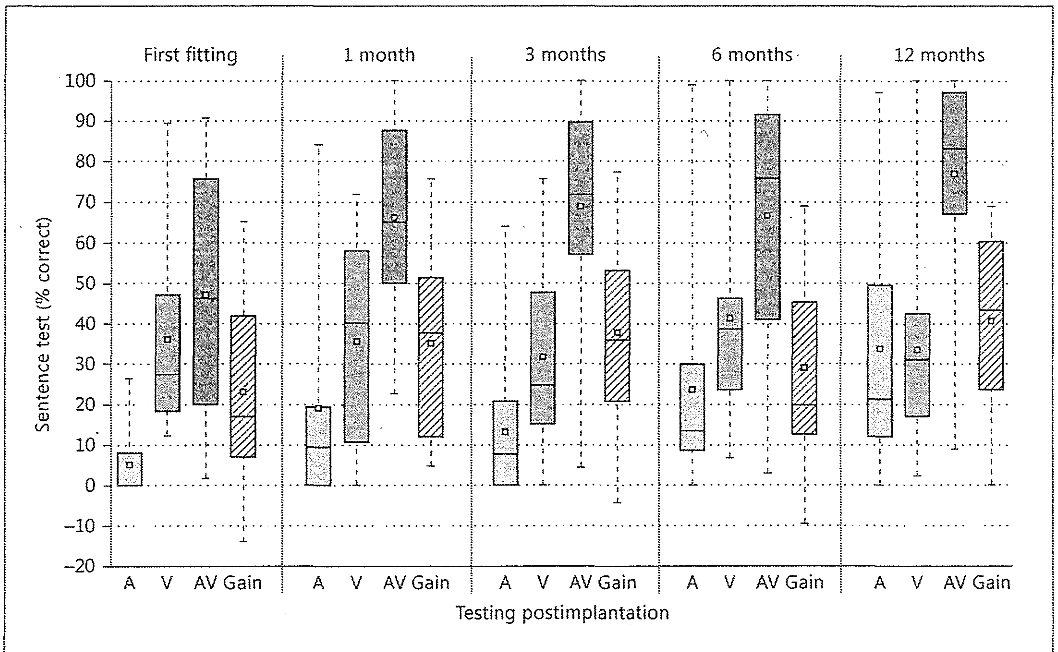

Fig. 3. Open-set speech recognition as determined by sentence testing in patients with an ABI after first fitting and 1, 3, 6 and 12 months postactivation. A: auditory only; V: visual only; AV: auditory-visual combined; Gain: AV-V. Boxplot whiskers depict sample minimum and maximum; the white square equals the mean value. Error bars represent standard deviation. Negative 'Gain' values represent patients who performed poorer in the combined auditory-only and visual-only conditions compared to the visual conditions.

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Table 2. Individual results of MTP words (words repeated correctly) of the auditory-only and auditory-visual test conditions

Subject ID	Auditory only					Auditory-visual				
	first fitting	1 month	3 months	6 months	12 months	first fitting	1 month	3 months	6 months	12 months
1	–	8	6	–	17	–	15	16	–	21
2	–	14	22	16	22	–	23	24	24	24
3	4	–	1	4	7	21	–	22	22	22
4	13	21	20	22	21	–	24	23	24	24
5	–	–	18	18	20	–	–	23	24	24
7	20	24	24	24	23	24	24	24	24	24
8	7	17	23	21	24	24	24	24	24	24
10	12	14	21	24	24	24	24	24	24	24
11	–	–	–	21	22	–	–	–	23	24
12	14	21	19	21	21	22	23	24	24	24
13	15	13	4	16	8	24	24	24	24	24
14	14	20	18	24	20	24	24	24	24	24
15	14	16	18	19	16	22	24	24	24	24
16	6	22	13	17	21	24	22	23	24	21
18	10	17	16	21	18	22	24	24	24	24
20	0	12	10	15	20	24	24	24	24	24
22	10	24	24	–	–	23	24	24	–	–
23	6	9	19	–	–	24	24	24	–	–
24	24	24	–	24	24	22	23	–	24	24
25	11	4	–	–	–	24	24	–	–	–
26	19	19	21	21	23	24	24	24	24	24
27	11	12	18	22	22	24	24	24	24	24
28	13	17	20	18	21	24	24	24	24	24
29	18	16	18	20	23	23	23	23	24	24
30[1]	19	15	16	16	12	24	24	24	24	24
31[1]	–	20	19	16	21	–	24	24	24	24
32	11	14	16	21	23	23	24	24	24	24
All data group										
n	21	24	24	23	24	21	24	24	23	24
Mean ± SD	11.7±6.4	15.4±5.3	16.1±6.2	17.9±4.8	19.6±4.2	23.2±1.0	23.2±2.1	23.2±2.1	23.8±0.6	23.6±1.0
Mean ± SD complete	12.1±6.0	15.8±3.0	16.7±3.4	18.8±2.4	19.2±3.4	23.4±0.8	23.7±0.6	23.8±0.4	24.0±0.0	23.8±0.8

Mean values ± SD are depicted for all data available (all data) and for the patients who performed the test at all test intervals (complete) under auditory-only (n = 17) and auditory-visual conditions (n = 16). SD = Standard deviation. [1] Revision cases.

Whitney U test: $p < 0.001$, $n = 8$) and the auditory-visual test conditions ($p = 0.001$, $n = 12$); no significant improvement was observed under visual-only test conditions ($p = 0.083$, $n = 6$).

Individual sentence test results under the auditory-only and auditory-visual conditions are shown in table 3. All subjects who performed the sentence test in the auditory-visual condition at first fitting (17 out of 26) were able to achieve at least some open-set speech understanding. Of the subjects available for the sentence test under auditory-visual conditions at first fitting and at 12-month testing, 11 out of 12 subjects performed better at the 12-month test interval. In the auditory-only condition 12 subjects performed the test at first fitting; 5 subjects achieved open-set speech understanding in this difficult test situation. After 12 months of ABI use 19 subjects could be tested, and all but 1 achieved open-set speech understanding. Overall, these data illustrate the improvement and learning ability over time

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Table 3. Individual sentence test results (% correct) of the auditory-only and auditory-visual test conditions

Subject ID	Auditory only					Auditory-visual				
	first fitting	1 month	3 months	6 months	12 months	first fitting	1 month	3 months	6 months	12 months
1	–	0.0	0.0	–	35.6	–	50.0	4.4	–	8.9
2	–	0.9	22.8	22.6	16.0	–	42.5	60.4	38.7	59.4
3	–	–	–	–	–	1.8	–	–	8.8	–
4	12.3	19.3	0.0	31.6	1.8	70.2	89.5	82.5	78.9	63.2
5	–	–	25.0	35.7	21.2	–	–	26.8	48.2	21.2
7	26.4	80.2	64.2	87.7	86.8	78.3	100.0	91.5	96.2	100.0
8	–	15.1	12.3	28.3	63.4	–	34.0	69.8	91.5	98.1
10	0.0	1.9	2.8	68.3	81.1	46.2	63.2	83.0	92.5	98.1
11	–	–	–	69.8	79.2	–	–	–	100.0	100.0
12	–	–	8.3	13.3	23.3	–	75.0	81.7	75.0	93.3
13	–	–	–	–	–	44.3	40.6	43.4	59.4	–
14	6.6	28.3	12.3	12.3	–	78.3	79.2	94.3	91.5	97.2
16	–	–	–	0.0	10.4	5.1	–	–	2.8	67.0
18	–	1.7	18.3	13.3	11.7	30.0	56.7	71.7	65.0	80.0
20	–	–	–	–	–	–	65.1	–	65.1	83.0
22	0.0	94.3	–	–	86.8	91.5	100.0	–	–	–
23	0.0	0.0	7.0	–	–	75.4	87.7	96.5	–	–
24	3.8	65.1	–	99.1	97.2	90.6	94.3	–	98.1	100.0
25	0.0	–	–	–	–	15.8	–	–	–	–
26	13.2	9.4	39.6	9.4	12.3	70.8	90.6	100.0	100.0	79.2
27	–	9.6	3.8	7.5	14.2	–	65.1	87.7	91.5	87.7
28	–	–	0.0	1.9	16.0	2.8	23.8	35.8	28.3	75.5
29	0.0	0.0	0.0	0.0	5.7	19.8	29.2	56.6	37.7	73.6
30[1]	0.0	1.9	0.0	0.0	0.0	35.8	52.8	57.5	35.8	48.1
31[1]	–	0.0	22.6	11.3	38.7	–	82.1	92.5	76.4	84.9
32	0.0	0.0	0.0	11.3	36.8	53.8	69.8	70.8	84.0	93.4
All data group										
n	12	17	18	19	20	17	21	19	22	21
Mean ± SD	5.2±8.3	19.9±30.2	13.3±17.1	27.6±30.8	36.9±32.8	47.7±31.3	66.2±23.6	68.8±26.2	66.6±30.1	76.8±25.3
Mean ± SD complete	7.4±10.3	16.1±29.1	15.2±26.0	29.8±35.0	32.1±37.6	48.6±26.2	65.5±25.6	74.4±20.0	71.0±27.5	80.8±16.9

Mean values ± SD are depicted for all data and for the patients who performed the test at all test intervals (complete) under auditory-only (n = 7) and auditory-visual conditions (n = 10). SD = Standard deviation. [1] Revision cases.

both on an individual and group basis. In summary, of the 19 subjects that could be tested at 12 months, under auditory-only conditions, a mean open speech perception of 37% was achieved. Under audio-visual conditions at 12 months the percentage of speech perception achieved was 77%.

To determine the benefit of ABI use over lip-reading alone, the auditory gain was calculated for the 'all data' group (fig. 3). At all test intervals the auditory gain was greater than the auditory-only performance, i.e. the sum of the results under auditory-only and visual-only combined was less than the performance under auditory-visual conditions. Furthermore, the auditory gain increased significantly over time from the first fitting to the 12-month test ($p = 0.008$).

Table 4. Questionnaire results

		n	%
About how long would you say it took for you to adjust to your ABI?	no time	3	21.4
	hardly any time	3	21.4
	moderate amount of time	5	35.7
	quite some time	3	21.4
	a very long time	0	0.0
How difficult was this adjustment for you?	not difficult	4	26.7
	somewhat difficult	7	46.6
	moderately difficult	2	13.3
	quite difficult	1	6.7
	very difficult	1	6.7
How would you rate the changes in your emotional state since you began wearing an ABI?	very positive	4	25.0
	somewhat positive	4	25.0
	neutral	7	43.7
	somewhat negative	1	6.3
	very negative	0	0.0
Has your ABI improved listening in individual conversation?	not at all	0	0.0
	hardly	1	6.3
	sometimes	6	37.5
	often	9	56.2
	not applicable	0	0.0
Has your ABI improved listening in groups?	not at all	2	12.5
	hardly	5	31.3
	sometimes	6	37.5
	often	2	12.5
	not applicable	1	6.3
Has your ABI improved listening in noisy environments?	not at all	4	26.7
	hardly	6	40.0
	sometimes	3	20.0
	often	1	6.7
	not applicable	1	6.7
How satisfied are you in general with your ABI?	very satisfied	5	33.3
	fairly satisfied	6	40.0
	adequately satisfied	4	26.7
	hardly satisfied	0	0.0
	not at all satisfied	0	0.0

Subjective Questionnaire

The subjective questionnaire was completed by 16 out of 27 subjects (table 4). Adjustment to the ABI was performed without difficulty in the majority of cases. The time needed to adjust to the ABI was 'minimal' or 'moderate' in 78.5% of the subjects. Accordingly, 73.3% reported that the adjustment to the ABI was 'not at all' or only 'somewhat' difficult for them. Only 1 subject (6.7%) felt that the adjustment was 'very difficult'; 50% of the subjects experienced 'very positive' or 'somewhat positive' changes in their emotional state since wearing the ABI. Again, only 1 subject (6.3%) reported a 'somewhat negative' experience. Ratings given by the users of the degree of help provided by the ABI in different listening situations showed the biggest benefit during individual conversation, with 93.7% of patients reporting improved listening abilities 'sometimes' to 'often'. Listening in groups was 'sometimes' to 'often' improved in 50.0% of users; however, 43.8% reported that they 'hardly' or 'not at all' bene-

fitted from the ABI during group conversation. The least benefit was experienced in noisy environments with only 26.7% of users reporting a benefit 'sometimes' to 'often' and 66.7% benefitting 'hardly' or 'not at all'. The questionnaire shows that, overall, 100% of patients were 'adequately satisfied' to 'very satisfied' with their ABI.

Discussion

In patients suffering from NF2 and a complete hearing loss, following tumor growth or removal, use of an ABI affords them some external auditory information. The extent of information provided is thought to facilitate lip-reading and the recognition of environmental sounds [9, 16–19, 22]. However, significant functional auditory-alone speech recognition is not expected [30–32]. Despite these limitations, NF2 patients with an ABI report varying degrees of benefit [22, 33–37]. The data presented herein shows that patients with an ABI demonstrate an initial improvement in SERT following first fitting. Likewise, MTP results show that under auditory-only conditions identification of words is enhanced with an ABI. Similarly, the capacity of the patients to determine sentences under auditory-only conditions was improved. This effect was apparent as early as 1 month after fitting. Sentence test performance under auditory-visual conditions was improved significantly. However, as no significant improvement in visual-only sentence testing was observed, the data in the present study suggests that NF2 patients can acquire benefits beyond enhanced lip-reading when using an ABI. This is likely to contribute to the patient's perception of the subjective benefits of using an ABI.

A period of acclimatization and learning facilitates the achievement of maximum benefit [9, 35]. However, the effects of NF2 on general health also need to be considered. In the present study follow-up testing was frequently interrupted or abandoned on account of patients suffering fatigue or on account of extrinsic factors as described by Otto et al. [9]. As follow-up is often perturbed by the pathological presentation of NF2, data were analyzed as a complete data set or following the exclusion of any individual(s) with missing data. Visual comparison of both data sets indicates that there is no apparent difference between the 'healthier' group and the group as a whole.

Another health-related consequence of ABI fitting is that electrical stimulation of the human brainstem carries the risk of nonauditory side effects. Most ABI patients experience these side effects, the solution to which is simply turning the electrode off [23]. Likewise, postoperative side effects of ABI activation determined the number of stimulatory electrodes programmed in this study. However, successful programming around the nonauditory sensations was possible in all patients included. The total number of active electrodes had no significant effect on the overall exceptional hearing performance of NF2 patients with an ABI presented in this study (data not shown) and the number of active electrodes over time appeared stable compared to the setting at first fitting. Similarly, Schmidt Goffi-Gomez et al. [38] showed that the number of active electrodes was not clinically related to outcome.

The current data clearly illustrate that with an ABI high levels of auditory performance were achieved in NF2 patients. NF2 patients with complete hearing loss implanted with the MED-EL COMBI 40+ or ABI showed an improvement in hearing performance after surgery. Closed-set MTP testing indicated that between the first fitting and the 12-month follow-up auditory-only word recognition was improved.

Of greater importance in the present study, NF2 patients with an ABI showed a significant improvement in auditory recognition when tested in an open-set task, i.e. sentence tests. The capacity of the patients to recognize sentences under auditory-only conditions over the entire test period (from first fitting to 12-month follow-up) improved and, likewise, their sentence

test performance under auditory-visual conditions. The improvement in sentence recognition was already apparent after 1 month. These data are of significant relevance because typically under auditory-only conditions ABI listeners are unable to recognize a significant amount of speech when tested in an open-set recognition task [13]. Using sound only from their ABI few NF2 patients recognized up to 20% of the words in sentences [13, 15]. The majority of NF2 patients recognize less than 5% of the words in sentences, even after several years of practice with the ABI [13, 39]. Moreover, as test materials become more complex, e.g. from word tests to open-set testing, performance with the ABI is thought to decline, especially under auditory-only conditions [17]. Nevison et al. indicate that although closed-set word identification tests show limited auditory-alone word identification, it would not be possible for ABI users to rely on their ABI alone. It was thought that the use of the ABI with lip-reading allowed the key words in conversation to be identified [17]. In contrast, the data presented in this study shows clearly that a large proportion of ABI users achieve valuable open-set speech understanding even if they rely exclusively on auditory-only input. Of all patients tested (all data) in the present study, the percentage of words recognized correctly in the sentence test using auditory-only cues was 20% after 1 month of ABI use. At the 12-month test interval this increased to 37%, which accounts for a considerably larger proportion than reported previously in the published literature [13, 39]. To investigate possible influencing factors comparative studies with a larger cohort of patients would be necessary. The current data is, however, substantiated with preliminary data collected in 2002 on the MED-EL ABI [22]. Furthermore, the results obtained with lip-reading in conjunction with the auditory input improved the benefit further than under auditory-only conditions. Thus, the data suggests that the exceptional benefit of the COMBI 40+ or ABI is in terms of comparatively real-life communication. The reasons for the difference in speech outcomes in the present study, compared to other published studies, have yet to be determined. We suspect the placing electrode used in MED-EL ABI systems has an effect. Once the placing electrode has been positioned intraoperatively, electrically evoked auditory brainstem responses can be recorded that aid the surgeon in the correct placement of the active ABI electrode. We presume that the test stimulation and intraoperative recording of electric auditory brainstem response may be one reason for better results using the MED-EL ABI. This should be a major point of investigation in future studies.

Moreover, the auditory gain as determined by open-set testing increased over time and was significantly greater after 12 months compared to the results at activation ($p = 0.008$). This suggests that the gain in speech recognition by NF2 patients with an ABI will potentially improve further over time. This is likely to occur due to a continued learning effect following ABI activation. Likewise, several authors indicate that the success of the NF2 patients with hearing loss in rehabilitation is most obvious upon long-term follow-up [20, 40].

However, some patients with an ABI in the present study showed a complete lack of improvement, whilst others managed a significant degree of rehabilitation. Other authors also report a significant degree of interindividual variability in the performance of NF2 patients with an ABI [13, 19]. Similarly, the study by Nevison et al. [17] in 2002 indicated that although most subjects did not achieve satisfactory auditory-alone open-set speech understanding, 2 patients of 17 tested received sufficient benefit from the ABI to an extent that allowed them to participate in conversation without the visual cues of lip-reading. The wide variation may in part be contributed to difficulties with follow-up, as mentioned briefly earlier. Frequently, the follow-up of patients with NF2 is perturbed due to changes in the status of the patient's health; in addition to nonauditory side effects, the most common of which are dizziness and ipsilateral tingling [41–43].

Despite these difficulties, the subjective benefits in patients with an ABI determined via questionnaire in the present study showed that overall all of the respondents were 'adequately'

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to 'very satisfied' with their ABI even after 6 months of follow-up. The majority reported improved listening ability 'sometimes' to 'often' in individual conversations. However, listening in noisy environments continued to pose a problem, as a case study of ABI use had previously indicated [20]. Similarly, listening in groups was 'sometimes' to 'not at all' improved in most cases. According to Colletti et al. [41], perceptual performance in ABI recipients can often vary considerably depending on the duration of the disease, the treatment of the disease and the number of active electrodes, in addition to their spatial configuration. However, in the context of the present study the data illustrates a relatively consistent improvement following auditory brainstem implantation with an overall satisfaction from 'adequately' to 'very satisfied', demonstrating the importance of providing some auditory input to patients deafened due to NF2.

In conclusion, the data presented herein indicate that NF2 patients with an ABI generally show improved closed-set speech recognition and, moreover, that patients show exceptional open-set sentence recognition. The acquisition of open-set speech recognition goes beyond the benefits achieved by lip-reading alone. Taking this into account and the young age of most NF2 sufferers, in addition to the unfortunate progressiveness of the disease, the capacity to restore some of the patient's hearing is of significant relevance, particularly in terms of quality of life.

References

1 Hanemann CO: Magic but treatable? Tumours due to loss of merlin. Brain 2008;131:606–615.
2 Evans DG, Moran A, King A, Saeed S, Gurusinghe N, Ramsden R: Incidence of vestibular schwannoma and neurofibromatosis 2 in the North West of England over a 10-year period: higher incidence than previously thought. Otol Neurotol 2005;26:93–97.
3 Samii M, Matthies C: Management of vestibular schwannomas. Hearing function in 1,000 cases. Neurosurgery 1997;40:248–262.
4 Samii M, Gerganov V, Samii A: Improved preservation of hearing and facial nerve function in vestibular schwannoma surgery via the retrosigmoid approach in a series of 200 patients. Neurosurgery 2006;105: 527–535.
5 Sughrue ME, Kaur R, Rutkowski MJ, et al: A critical evaluation of vestibular schwannoma surgery for patients younger than 40 years of age. Neurosurgery 2010;67:1646–1654.
6 Tringali S, Ferber-Viart C, Fuchsmann C, Buiret G, Zaouche S, Dubreuil C: Hearing preservation in retrosigmoid approach of small vestibular schwannomas: prognostic value of the degree of internal auditory canal filing. Otol Neurotol 2010;31:1469–1472.
7 Tran Ba Huy P, Kania R, Frachet B, Poncet C, Legac MS: Auditory rehabilitation with cochlear implantation in patients with neurofibromatosis type 2. Acta Otolaryngol 2009;129:971–975.
8 Vincenti V, Pasanisi E, Guida M, Di Trapani G, Sanna M: Hearing rehabilitation in neurofibromatosis type 2 patients: cochlear versus auditory brainstem implantation. Audiol Neurotol 2008;13:273–280.
9 Otto SR, Brackmann DE, Hitselberger WE, Shannon RV, Kuchta J: Multichannel auditory brainstem implant: update on performance in 61 patients. J Neurosurg 2002;96:1063–1071.
10 Brackmann DE, Hitselberger WE, Nelson RA, et al: Auditory brainstem implant. I. Issues in surgical implantation. Otolaryngol Head Neck Surg 1993;108:624–633.
11 Edgerton BJ, House WF, Hitselberger WE: Hearing by cochlear nucleus stimulation in humans. Ann Otol Rhinol Laryngol Suppl 1982;91:117–124.
12 Shannon RV, Fayad J, Moore J, et al: Auditory brainstem implant. II. Post-surgical issues and performance. Otolaryngol Head Neck Surg 1993;108:634–642.
13 Colletti V, Shannon RV, Carner M, Veronese S, Colletti L: Progress in restoration of hearing with the auditory brainstem implant. Prog Brain Res 2009;175:333–345.
14 Skarzynski H, Behr R, Lorens A, Podskarbi-Fayette R, Kochanek K: Bilateral electric stimulation from auditory brainstem implants in a patient with neurofibromatosis type 2. Med Sci Monit 2009;15:CS100–CS104.
15 Sollmann WP, Laszig R, Marangos N, et al: Electrical stimulation of the cochlear nucleus. First results of the European auditory brainstem implant clinical trial. 11th International Congress of Neurological Surgery, Amsterdam, 1997.
16 Matthies C, Thomas S, Moshrefi M, et al: Auditory brainstem implants: current neurosurgical experiences and perspective. J Laryngol Otol Suppl 2000;114:32–36.

17 Nevison B, Laszig R, Sollmann WP, et al: Results from a European clinical investigation of the nucleus multichannel auditory brainstem implant. Ear Hear 2002;23:170–183.
18 Behr R, Müller J, Shehata-Dieler W, et al: The high rate CIS auditory brainstem implant for restoration of hearing in NF2 patients. Skull Base 2007;17:91–107.
19 Grayeli AB, Kalamarides M, Bouccara D, Ambert-Dahan E, Sterkers O: Auditory brainstem implant in neurofibromatosis type 2 and non-neurofibromatosis type 2 patients. Otol Neurotol 2008;29:1140–1146.
20 Maini S, Cohen MA, Hollow R, Briggs R: Update on long-term results with auditory brainstem implants in NF2 patients. Cochlear Implants Int 2009;10:33–37.
21 Neff BA, Wiet RM, Lasak JM, et al: Cochlear implantation in the neurofibromatosis type 2 patient: long-term follow-up. Laryngoscope 2007;117:1069–1072.
22 Jackson KB, Mark G, Helms J, Mueller J, Behr R: An auditory brainstem implant system. Am J Audiol 2002;11: 128–133.
23 Shannon RV: Threshold functions for electrical stimulation of the human cochlear nucleus; in Kent RD (ed): The MIT Encyclopedia of Communication Disorders. Massachusetts, MIT Press, 2004, vol 40, pp 427–429.
24 Otto SR, Shannon RV, Brackmann DE, Hitselberger WE, Staller S, Menapace C: The multichannel auditory brain stem implant: performance in twenty patients. Otolaryngol Head Neck Surg 1998;118:291–303.
25 Vincent C, Zini C, Gandolfi A, et al: Results of the MXM Digisonic auditory brainstem implant clinical trials in Europe. Otol Neurotol 2002;23:56–60.
26 Fayad JN, Otto SR, Brackmann DE; in Møller AR (ed): Cochlear and Brainstem Implants. Basel, Karger, 2006, vol 64, pp 144–153.
27 St. Clair EG, Golfinos JG, Roland JT: Auditory brainstem implants; in Waltzmann SB, Roland JT (eds): Cochlear Implants. New York, Thieme, 2006, pp 222–229.
28 Kuchta J, Otto SR, Shannon RV, Hitselberger WE, Brackmann DE: The multichannel auditory brainstem implant: how many electrodes make sense? J Neurosurg 2004;100:16–23.
29 Wilson BS, Finley CC, Lawson DT, Wolford RD, Eddington DK, Rabinowitz WM: Better speech recognition with cochlear implants. Nature 1991;352:236–238.
30 Laszig R, Aschendorff A: Cochlear implants and electrical brainstem stimulation in sensorineural hearing loss. Curr Opin Neurol 1999;12:41–44.
31 Ebinger K, Otto S, Arcaroli J, Staller S, Arndt P: Multichannel auditory brainstem implant: US clinical trial results. J Laryngol Otol 2000;114(suppl 27):50–53.
32 Toh EH, Luxford WM: Cochlear and brainstem implantation. Otolaryngol Clin North Am 2002;35:325–342.
33 Lustig LR, Yeagle J, Driscoll CLW, Blevins N, Francis H, Niparko J: Cochlear implantation in patients with neurofibromatosis type 2 and bilateral vestibular schwannoma. Otol Neurotol 2006;27:512–518.
34 Colletti V: Auditory outcomes in tumor vs. nontumor patients fitted with auditory brainstem implants. Adv Otorhinolaryngol 2006;64:167–185.
35 Lenarz M, Matthies C, Lesinski-Schiedat A, et al: Auditory brainstem implant. Part II. Subjective assessment of functional outcome. Otol Neurotol 2002;23:694–697.
36 Lenarz T, Moshrefi M, Matthies C, et al: Auditory brainstem implant. Part I. Auditory performance and its evolution over time. Otol Neurotol 2001;22:823–833.
37 Sanna M, Di Lella F, Guida M, Merkus P: Auditory brainstem implants in NF2 patients: results and review of the literature. Otol Neurotol 2012;33:154–164.
38 Schmidt Goffi-Gomez MV, Megalhaes AT, Brito-Neto R, Tsuji RK, de Queiroz Telles Gomes M, Ferreira Bento R: Auditory brainstem implant outcomes and MAP parameters: report of experiences in adults and children. Int J Pediatr Otorhinolaryngol 2012;76:257–264.
39 Schwartz MS, Otto SR, Shannon RV, Hitselberger WE, Brackmann DE: Auditory brainstem implants. Neurotherapeutics 2008;5:128–136.
40 Lesinski-Schiedat A, Frohne C, Illg A, et al: Auditory brainstem implant in auditory rehabilitation of patients with neurofibromatosis type 2: Hannover program. J Laryngol Otol 2000;114:15–17.
41 Colletti V, Carner M, Miorelli V, Guida M, Colletti L, Fiorino F: Auditory brainstem implant (ABI): new frontiers in adults and children. Otolaryngol Head Neck Surg 2005;133:126–138.
42 Otto SR, Brackmann DE, Hitselberger WE, Shannon RV: Brainstem electronic implants for bilateral anacusis following surgical removal of cerebello-pontine angle lesions. Otolaryngol Clin North Am 2001;34:485–499.
43 Otto SR, Brackmann DE, Hitselberger WE: Auditory brainstem implantation in 12- to 18-year olds. Arch Otolaryngol Head Neck Surg 2004;130:656–659.

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新生児聴覚スクリーニングの偽陽性率を減らすための試行制度の検討

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要旨：新生児聴覚スクリーニングNHSの有用性は確立されているが，refer例において精密検査で正常聴力であった率（refer偽陽性率）は，ほぼ40%前後と高い．先天性代謝疾患のマス・スクリーニング偽陽性率が0.01%以下の値であるのに対して，4自治体によるNHS事業報告ではNHSのマス・スクリーニング偽陽性率は0.0842〜0.1482%と8倍以上高かった。このNHSの高い偽陽性率を改善するため，当院では，入院中の確認NHS検査でもreferであった例に対しては，1カ月検診時にAABRによるNHS再検査を施行するシステムを試行してきた。導入時から5年間の1849例のデータを用いてretrospectiveに検討した結果，初回NHSのrefer偽陽性率は76%（19/25），退院前の確認NHSの偽陽性率も40%（4/10）であったが，1カ月時の検診時に行った最終NHS検査での偽陽性率は0%（0/6）にまで減じた。結論として，入院中に確認NHSでもreferであった新生児に対して，同一施設にての1カ月検診時に最終NHS検査を行い，その結果で耳鼻咽喉科の精密検査機関を受診させる方式はNHSのrefer偽陽性率を最小限にし，両親と新生児が受ける負担，不利益の多くを排除できると考える。検討課題とその対処法についても述べた。

ーキーワードー
新生児聴覚スクリーニング，再検査refer，偽陽性

はじめに

自動聴性脳幹反応AABRや耳音響放射OAEによる新生児聴覚スクリーニング（Newborn hearing screening以下NHS）は，わが国では1998年から厚生科学研究（子ども家庭総合研究事業）「新生児期の効果的な聴覚スクリーニング方法と療育体制に関する研究」によって開始された[1)]。2001年よりマス・スクリーニングとして，NHSモデル事業として行われた[2)]。わが国での普及状況は，2005年の時点では産科施設全体の62%，個人病院と診療所の70%，大学病院の40%の施設で導入されており[3)]，難聴の早期発見，そして補聴器・人工内耳装用などの早期介入を可能にする点で，その有用性は明らかとなっている[2,3)]。

一方，NHSに伴う問題点として，出産後間もない不安定な心身である母子愛着形成前の重要な時期に，わが子が難聴の疑いありとされ，さらに精密検査機関への受診を指示された両親に，多くの精神的あるいは心因的症状が生じることが知られている[4)]。

また，日本耳鼻咽喉科学会福祉医療・乳幼児委員会による2年に一度の実態調査が行われている[5,6,7)]が，精密検査機関に紹介され聴性脳幹反応ABR，聴性定常反応ASSRなどの他覚的聴覚検査を受けた結果，聴力が正常範囲内であった者の率（これは正

常聴力者/refer者で求められ，これを以下refer偽陽性率と仮称する）について計算してみると，後述するように，いずれの調査においても，精密検査機関に紹介されたうちの約40％が正常聴力範囲内にあり，refer偽陽性率は約40％とかなり高いことが判明した。したがって，NHSの有効性を評価するために，まずNHSの偽陽性を明らかにし，高い偽陽性率を改善することが求められる。

そこで当院では，入院中に初回NHS referとなった新生児に対して，確認NHSを行いreferであった場合には，１カ月検診時の最終NHSの結果により精密聴力検査を行うか否かを判定するシステムを試行してきた。導入時から５年間のデータを用いて，これによって，どの程度までrefer偽陽性率を減らすことが出来たかをretrospectiveに検討した。

また，スクリーニング全対象者数における偽陽性率を求めることが他のマス・スクリーニング検査との比較を行う上で重要である[8]が，日本耳鼻咽喉科学会福祉医療・乳幼児委員会による実態調査では全対象者数が明らかではないという難点があった。そこで，過去に報告された自治体によるNHS事業のうち，対象者数が明らかな報告の再解析を行い，NHSのマス・スクリーニングとしての偽陽性率を求め，他の新生児マス・スクリーニング検査との比較を行った。

対象と方法

１．当院でのNHSのデータ解析

虎の門病院には2006年からAABR装置として，Natus社製ALGO２カラーが導入され，希望家族を対象に自己負担（５千円）でNHSが開始された。2006～2010年の５年間に虎の門病院産科で出生した1945例のうち，NHSを希望した，あるいはハイリスクのために医療側からNHSを勧められた1849例が解析対象となった。NHSは入院中にAABR装置だけによって行われた。スクリーニング音圧は35 dBnHLであった。

初回検査でのrefer例に対しては，入院中に２回目の確認NHS検査を行い，それでもreferであった場合は１カ月検診時に同じ機種による最終NHSを産科外来の比較的静かな部屋で行った。この検査は耳鼻咽喉科としての受診ではなく，費用は初回分の自己負担金額に含まれるものとして，新たな請求を行わなかった。

１カ月目の最終NHS検査でもreferと判定された例は，その時点で当院の耳鼻咽喉科に紹介され，精密検査が予約された。そして，ほぼ１～２カ月後，すなわち２～３カ月の月齢時に，防音室で睡眠下に聴性定常反応ASSR（使用機器はAudera），誘発音響放射DPOAE（使用機種ILO292-USB）による他覚的精密検査を保険診療で行った。

ASSRでは250，500，1k，2k，4kHzの刺激音に対して，左右別かつ各周波数毎に反応域値が求められた後に，月齢に伴う補正が機器により自動でなされ，検査児の推定域値が表示された。DPOAEでは1～6kHzにおける反応パワースペクトル（DPグラム）が表示された。そして当院における聴力正常であった乳児のASSR推定域値の分布範囲から，検査児の難聴の有無が判定された。

２．マス・スクリーニングとしての偽陽性率

全対象者数Aが明らかな長野県[9]，岡山県[10]，栃木県[11]，鳥取県[12]の４自治体による最近のNHS事業について，refer者数B，精密検査で判明した難聴者数（少なくとも，左右のいずれかが難聴であった者）C，難聴者の率C/A，正常聴力者数D，refer偽陽性率D/B，マス・スクリーニングとしての偽陽性率D/Aをそれぞれ計算した。

結　果

１．当院でのNHSのデータ解析

当院におけるNHSの受診率は，検査費用が自己負担であるにも関わらず，95％（1849/1945）と，きわめて高率であった。これは，産科におけるペアレンツクラスでの講義に，NHSの意義が話されているためと考えられた。

表１に示すように，入院中の初回NHSでのreferは25例であったが，入院中の確認NHSでのreferは10例に減少し，産科外来で１カ月検診時に行われた最終NHSでうち４例がpassし，referは６例にまで減少した。

そして，これらの６例は，表２に示したように，全例がその後に当院の耳鼻咽喉科で行われたASSR，DPOAEによる精密検査およびその後のフ

表1　当院での2006年～2010年までのNHS refer例とその後の精密検査結果

年度	総出生数	NHS受診者数	初回 refer	入院中の確認検査でも refer	1カ月目の検診時NHSでも refer	精密検査受診（うち難聴あり）	referが偽陽性であった例
2006	357	325	6	3	2	2(2)	0
2007	348	330	5	2	1	1(1)	0
2008	408	390	5	1	1	1(1)	0
2009	455	428	4	1	0	0	0
2010	377	376	5	3	2	2(2)	0
計	1945	1849	25 (1.35%)	10 (0.54%)	6 (0.32%)	6(6) (0.32%)	0

表2　1カ月目でNHS referであった6例の精密聴力検査の結果

患者	年度	初回 NHS	1カ月後 NHS	精密検査結果と現在の状況
1	2006	両側 refer	左 refer（40dB）	外耳道閉鎖（両側 50dB） 当科外来フォロー中
2	2006	両側 refer	左 refer（40dB）	両側伝音難聴 （右 60dB，左 55dB） 当院外来フォロー中
3	2007	両側 refer	両側 refer	両側 90dB 21トリソミー，食道閉鎖症にて 他院にて手術他院にてフォロー中
4	2008	右 refer 左 pass	右 refer（70dB）	ASSR にて右 90dB の難聴。 他院にてフォロー中
5	2010	右 refer 左 pass	右 refer（35dB）	ASSR にて右 95dB の難聴。 当院外来フォロー中
6	2010	両側 refer	右 refer（40dB） 左 refer（35dB）	ASSR にて難聴。（低音域 30dB，高音域 50dB） 当院外来フォロー中

ォローアップ検査でも，最終的に一側あるいは両側の50～70dBの難聴と診断された。すなわち，この6例ではreferが偽陽性であった例はなかったことになる。対象者における難聴者の率は0.32%（6/1849）であった。

したがって，初回NHS検査でのrefer偽陽性（正常聴力者/refer者）率は76%（19/25），退院前の確認NHSの偽陽性率も40%（4/10）であったが，1カ月時の検診時に行った最終NHS検査陽性例を対象にして精密検査を行った場合，そのrefer偽陽性率は0%（0/6）にまで減じた。

なお，pass児の追跡調査から，難聴を見逃した偽陰性率も0%であった。

2．マス・スクリーニングとしての偽陽性率

結果を表3に示した。長野県，岡山県，栃木県，鳥取県の順に，NHS全対象者における難聴者の率C/Aはそれぞれ，0.13%，0.17%，0.54%，0.31%であった。この値は当院の難聴者の率と大差がなかった。refer偽陽性率D/Bはそれぞれ39.8%，26.9%，21%，28%であった。マス・スクリーニングとしてのNHS偽陽性率D/Aは，それぞれ，0.0842%，0.1368%，0.1452%，0.1482%であった。

考　察

1．わが国でのNHSのrefer偽陽性率

田丸ら[8]は新生児スクリーニング検査の有効性を検討する場合には，その偽陽性率が検討されなけれ