Vestibular PREHAB and gentamicin before schwannoma surgery may improve long-term postural function

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ABSTRACT

Background: Unilateral vestibular deafferentation (uVD), as performed in vestibular schwannoma surgery, results in a chronic vestibular deficit, though most of the insufficiency can be compensated by other sensory input. By vestibular training (prehabituation) performed before surgery, motor adaptation processes can be instigated before the actual lesion. The adaptation processes of the altered sensory input could be affected if the vestibular ablation and surgery were separated in time, by pretreating patients who have remaining vestibular function with gentamicin.

Objective: To determine whether presurgical deafferentation would affect postsurgery postural control also in a long-term perspective (6 months).

Method: 41 patients subjected to trans-labyrinthine schwannoma surgery were divided into four groups depending on the vestibular activity before surgery (with no clinical significant remaining function n = 17; with remaining function n = 8), whether signs of central lesions were present (n = 10), and if patients with remaining vestibular activity were treated with gentamicin with the aim to produce uVD before surgery (n = 6). The vibratory posturography recordings before surgery and at the follow-up 6 months after surgery were compared.

Results: The subjects pretreated with gentamicin had significantly less postural sway at the follow-up, both compared with the preoperative recordings and compared with the other groups.

Conclusion: The results indicate that by both careful sensory training and separating the surgical trauma and the effects of uVD in time, adaptive processes can develop more efficiently to resolve sensory conflicts, resulting in a reduction of symptoms not only directly after surgery but also perhaps up to 6 months afterwards.

Patients scheduled for vestibular schwannomas are subject to challenged rehabilitation processes, partly due to the intracranial surgery but also to the effects of acute unilateral vestibular deafferentation (uVD). Acute uVD results in vertigo, malaise and postural imbalance, beside the physiological manifestations of spontaneous nystagmus, ocular torsion and disturbances of perceived vertical and horizontal.[1] Vestibular deafferentation also results in cognitive impairments[2–4] and, if performed bilaterally, results in hippocampal atrophy.[4] Due to the usually slow growth rate of the tumours, the remaining function of the vestibular system before surgery differs considerably among patients, giving a varying spectrum of postsurgery illness and need for rehabilitation. The status of the vestibular system should be carefully assessed preoperatively. Recently a treatment procedure was reported, in which patients who had remnants of vestibular function before surgery were ablated by installing gentamicin in the middle ear.[5 6] The treatment is aimed at achieving total uVD before surgery, giving the patients time to adapt to the altered sensory input. The symptoms and manifestations of uVD subside with time with the development of vestibular compensation,[7] dependent on the central nervous system (CNS).[8] Although the symptoms decrease with time, the responses to passively imposed vestibular stimuli do not recover, and some other sensory input must compensate for the vestibular deficiency.[9] The ability to adapt and modify postural strategies to altered afferent sensory input (as in vestibular disorders), as well as to different external constraints, is essential for an operational postural control system. Postural control is maintained by both feedback and feed-forward mechanisms.[10] Feedback control depends on sensory inputs (vision, vestibular and somatosensory) that are processed, integrated and weighted to their relative importance and context in the CNS.[11] Feed-forward mechanisms involve the concept of ''internal models,'' whose output consists of preformed neuromuscular strategies activated in given situations automatically or voluntarily (anticipated movement). Learning how to withstand a postural perturbation, such as vibratory proprioceptive stimulation, seems to follow the general paradigm of memory formation with a consolidation of a short-term memory into a longer-lasting memory.[12] The generated response corresponds to an internal model designed to control posture when exposed to vibratory stimulation, and most likely involves areas within the CNS involved in adaptation and learning, that is cerebellum and hippocampus.[13 14] Surgery, even minor abdominal, leads to inflammation in the CNS, indicated by elevated cytokines in the hippocampus and cerebellum, resulting in memory impairment when learning new tasks.[15] It can thus be conceivable that surgery and deafferentation performed at the same time would lead to delayed or impaired compensation and that separating the different traumas in time would generate a more efficient recalibration process of the altered sensory information. In the present study, we aimed to assess the recordings with vibratory proprioceptive stimulation before and after surgery of patients with varying vestibular function from the disease,

with the specific aim to examine whether presurgical deafferentation and sensory training would affect postsurgery postural control also in the longer term, here up to 6 months after surgery.

MATERIAL AND METHOD

Subjects

Between 2001 and 2007, 82 patients were subjected to translabyrinthine vestibular schwannoma surgery at Lund University Hospital. Only this surgical approach was considered, as the procedure comprises a total destruction of the inner ear and is considered to be the method of choice for small tumours when no hearing preservation is required. In half of the patients (n = 41) the posturography data both pre- and postsurgery could be retrieved, and these patients were included in the study. The vestibular function was assessed both before and after surgery, with a video-recorded head impulse test of all three canals of each ear,[16] bithermal calorics, vestibular evoked myogenic potential measured on the sternocleidomastoid muscle (cVEMP), subjective horizontal and vertical, rod and frame tests, posturography, eye movement analyses and audiometric with pure tone and speech discrimination evaluation. The patients were divided into four groups depending on the clinical status before and after surgery (fig 1).

Group 1 (n = 17, 11 male and six female, median age 58, range 33 to 71) consisted of patients with no clinically significant vestibular function, defined as a pathological head impulse test in all planes of the semicircular canals, an eye velocity of <7.5°/s (mean 3.0, range 0.5 to 4.9)[17] during calorics and no registered cVEMP of the affected ear. Group 2 (n = 8, four males and four females, median age 43.5, range 26 to 72) consisted of patients with an intact head impulse test and/or a recorded eye velocity >7.5°/s (mean 10.0, range 1.9 to 19.4) during calorics. cVEMP varied but was intact in two patients. The head impulse test was intact in seven patients. Group 3 (n = 10, six male and four female, median age 52.5, range 28 to 65) consisted of patients who, beside the vestibular disorder, showed signs of central nervous disorder during the presurgical assessment (ataxia, pathological voluntary eye movements, tilted subjective horizon to the contralateral side, Bruns nystagmus, etc) or signs of severe ataxia postsurgery. The vestibular function before surgery varied from clinically total uVD to normal. Calorics gave a mean of 6.5 and range of 0.9 to 18.6°/s. The head impulse test was intact in five patients. Group 4 (n = 6, four male and 2 female, median age 50, range 36 to 66) consisted of patients

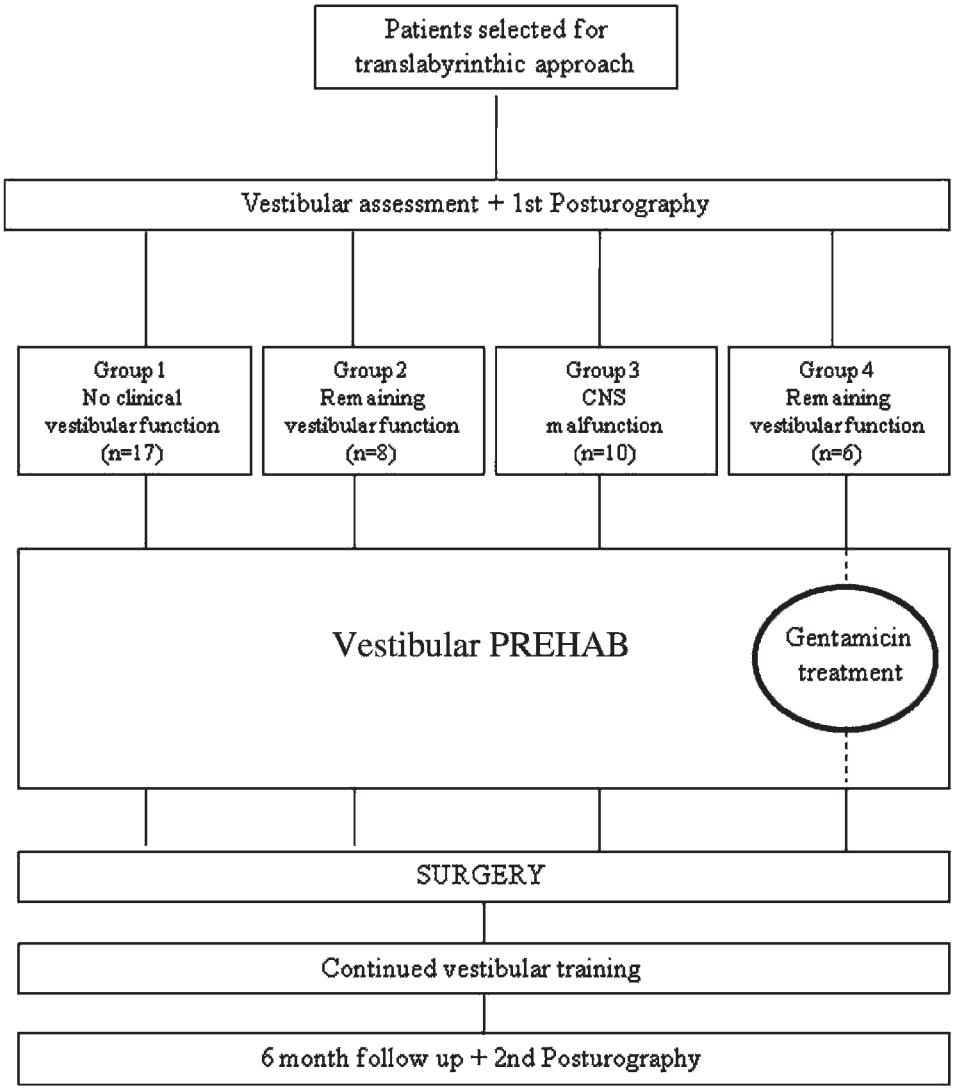

Figure 1 Table of sequences describing group division and the interventions for each group. "PREHAB" is described further in the method section, and the exercises are described in detail in fig 2. CNS, central nervous system.

with intact vestibular function that were pretreated with gentamicin before surgery (for details see table 1). This regime was offered to all patients with remaining vestibular function after year 2003. All but one patient had measurable remnants of vestibular function of the affected ear. That patient suffered from vertiginous attacks and was regarded as having remaining vestibular function on the affected side. Calorics gave a mean of 11.8 and range of 0.5 to 25.4°/s.

The rationale behind the patient subdivision was that the vestibular function presurgery could affect the outcome on posturography follow-up, and that lesions within CNS could affect compensation processes as well as posturographic measurements, and as such be confounding. The largest tumour extrameatal diameter differed between the groups as would be expected, with the largest in group 3 (median 29 mm, range 10 to 40 mm) and the smallest in group 2 (median 15.5 mm, range 11 to 33 mm) and group 4 (median 19 mm, range 6 to 25 mm). Group 1 had a median tumour size of 22 mm (range 5 to 43 mm).

Patients with a remaining vestibular system function after 2003 were offered presurgical deafferentation and accepted. They received two to four trans-tympanic injections of approximately 0.3 to 0.4 ml of gentamicin at each injection over two consecutive days.

Vestibular PREHAB

All patients were instructed to execute the home-based vestibular training programme (fig 2), adopted for patients with acute vestibular loss, 14 days before surgery and continue the training programme in the first postoperative weeks, until they considered themselves free of symptoms. For patients receiving gentamicin, the "PREHAB" constituted of 14 days of training, after which gentamicin was installed in the middle ear on the tumour side. The training continued during installations and afterwards as the ototoxic effect of the gentamicin gradually took effect.[18] The subjects were encouraged to perform the programme for at least 6 weeks, after which they were assessed and considered compensated. The exercises in vestibular "PREHAB" are identical to the vestibular training programme, and the term should ideally be restricted to be used in patients who had a remaining vestibular function prior to surgery/gentamicin treatment (groups 2 and 4). However, to avoid confusion, we term all sensory training performed prior to an intervention "PREHAB" (fig 1).

Posturography

Postural control was evaluated by perturbing stance while standing on a force platform (400×400×75 mm) equipped with six strain-gauge sensors. Forces and torques actuated by the feet were recorded with six degrees of freedom by a force platform. Data were sampled at 50 Hz by a computer equipped with a 12-bit analogue-to-digital converter. The vibrations were applied to the muscles by two cylindrical vibrators (0.06 m long and 0.01 m in diameters), held in place with an elastic strap around each leg. The vibration amplitude was 1.0 mm amplitude at a constant frequency of 85 Hz. The vibratory stimulation was executed according to a computer-controlled pseudorandom binary sequence (PRBS) schedule[19] for 205 s by turning on/off the vibratory stimulation. The PRBS schedule was composed of stimulation shift periods of random duration between 0.8 and 6.4 s (yielding an effective bandwidth of 0.1–2.5 Hz). Thus, the designated PRBS stimuli covered a broad power spectrum, and the randomised stimulation reduced the opportunity to make anticipative and pre-emptive adjustments.

After information about the test procedure, the subjects were instructed to stand erect but not "at attention," with arms crossed over the chest and feet at an angle of about 30° open to the front and the heals approximately 3 cm apart. Two tests were conducted at each trial, with the eyes open, fixating on a

Table 1 Vestibular status and timing of the posturography recordings in group 4, pretreated with gentamicin

Patient	Vestibular function prior to gentamicin	Gentamicin treatment	Vestibular function after gentamicin	Posturography assessment
1	Sacculus+posterior SCC	Three installations 6 months prior to surgery	None	1: 1 week prior to gentamicin 2: 6 weeks postgentamicin 3: 5 months postsurgery
2	Anterior and lateral SCCs+utriculus	Three installations 5 months prior to surgery	None	1: 2 months prior to gentamicin 2: 5 months postgentamicin 3: 1 week postsurgery 4: 6 months postsurgery
3	Sacculus+all SCCs	Four installations 3 months prior to surgery	None	1: 1 month prior to gentamicin 2: 6 weeks postgentamicin 3: 6 months postsurgery
4	Sacculus—all SCCs	Three installations 3 months prior to surgery	None	1: 3 weeks prior to gentamicin 2: 6 weeks postgentamicin 3: 1 week postsurgery 4: 6 months postsurgery
5	None, but vertiginous attacks deemed to be caused by the affected ear	Four installations 3 months prior to surgery	None	1: 1 week prior to gentamicin 2: 7 months postsurgery
6	All SCCs	Two installations 3 months prior to surgery	None	1: 1 week prior to gentamicin 2: 2 months postgentamicin 3: 8 months postsurgery

SCC, semicircular canal.

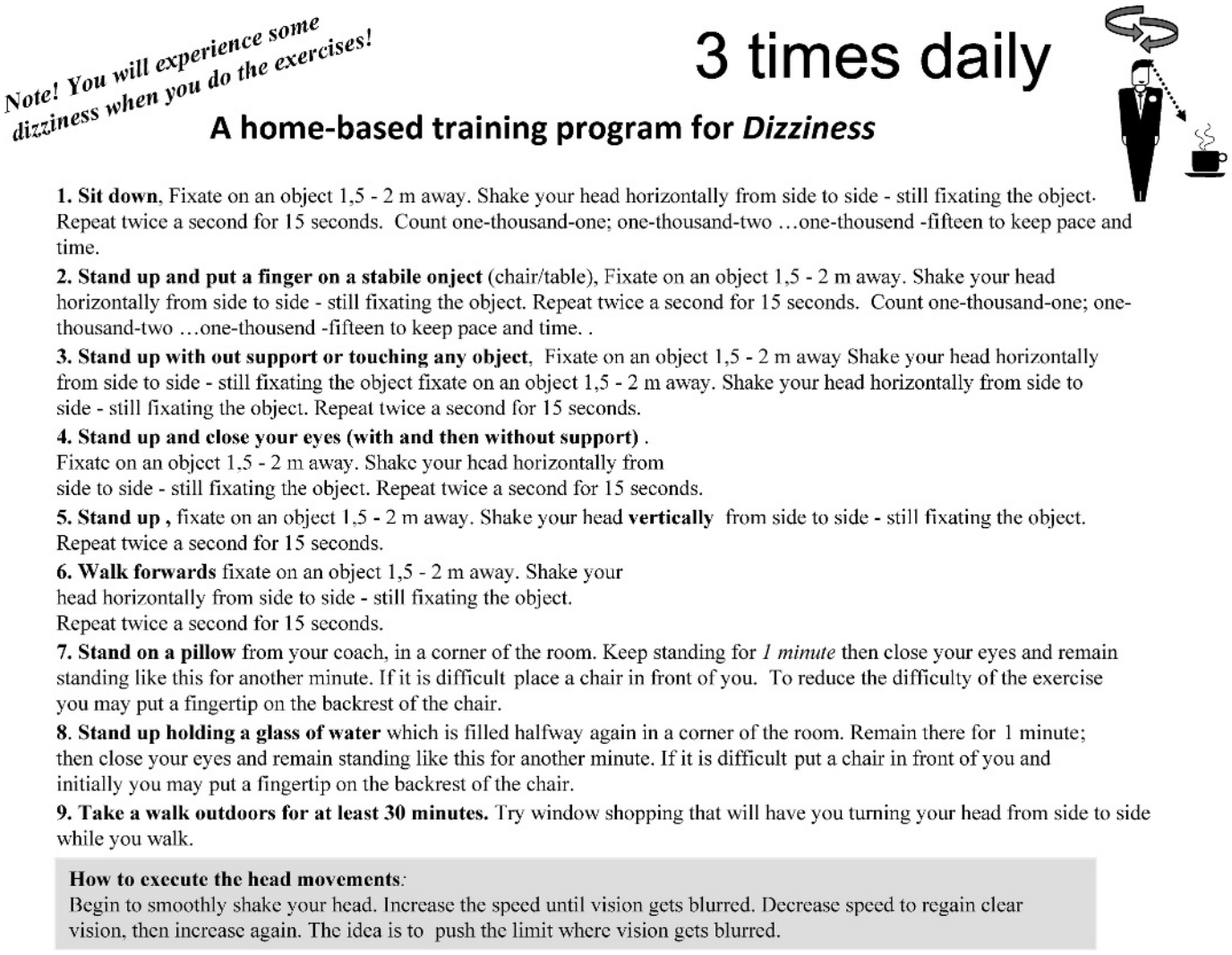

Figure 2 Vestibular training programme constituting the vestibular "PREHAB," and the sensory training before and after surgery, as well as after gentamicin treatment, which all patients were encouraged to execute. The principle of the exercises is to use sensory mismatch to enforce recalibration of vestibular reflexes on a cellular level.[25]

mark on the wall at a distance of 1.5 m, and the eyes closed. The test order followed our set clinical procedure, always starting with the eyes open followed by the eyes closed. In order to minimise the external disturbances for the test subjects, the recordings were performed while the test subjects listened to classical music relayed through headphones.

Patients in groups 1–3 were tested before surgery and after surgery (with the exception of one patient who was tested twice before surgery due to a prolonged time period between the initial examination and surgery). Patients in group 4 were tested two to four times, as shown in table 1, because of the necessity of evaluating the gentamicin-treatment efficacy.

Data analysis

The variance of anteroposterior body sway was calculated for five periods for each test: a quiet stance period (0–30 s) before stimulation was applied, and for four periods (1–4) during the stimulation (30–80, 80–130, 130–180 and 180–230 s, respectively). Regression analysis of the torque variance showed a relation to the test subjects' squared mass and squared height. The torque variance data were therefore normalised by squared mass and squared height. As vibratory stimulation applied to calf muscles mainly affects muscles predominantly active in the anteroposterior direction,[20] only those responses were analysed. Statistics was calculated using non-parametric Wilcoxon for paired data (groups) and Mann–Whitney for unpaired data (between the groups). Non-parametric statistics were used, since some values were not normally distributed, and a normal distribution could not be obtained after log transformation.

RESULTS

In fig 3A,B, the normalised sway variance in the anteroposterior direction for all groups is demonstrated. Groups 1–3 did not decrease their induced torque variance from before surgery to the follow-up 6 months after surgery in either test condition (except for group 3, period 3 with eyes open). Group 4, however, decreased the induced torque significantly after surgery in both test conditions (closed eyes period 1–4, and open eyes period 1, 3 and the quiet stance period) as shown in the fig 3A,B.

The torque variance in groups 1–3 could not be separated from group 4 statistically before surgery regardless of the test condition. At the follow-up, group 1 had significantly more sway than group 4; with eyes closed in period 1 and 4 ($p<0.05$) and period 3 ($p<0.01$), and with eyes open in period 1–3

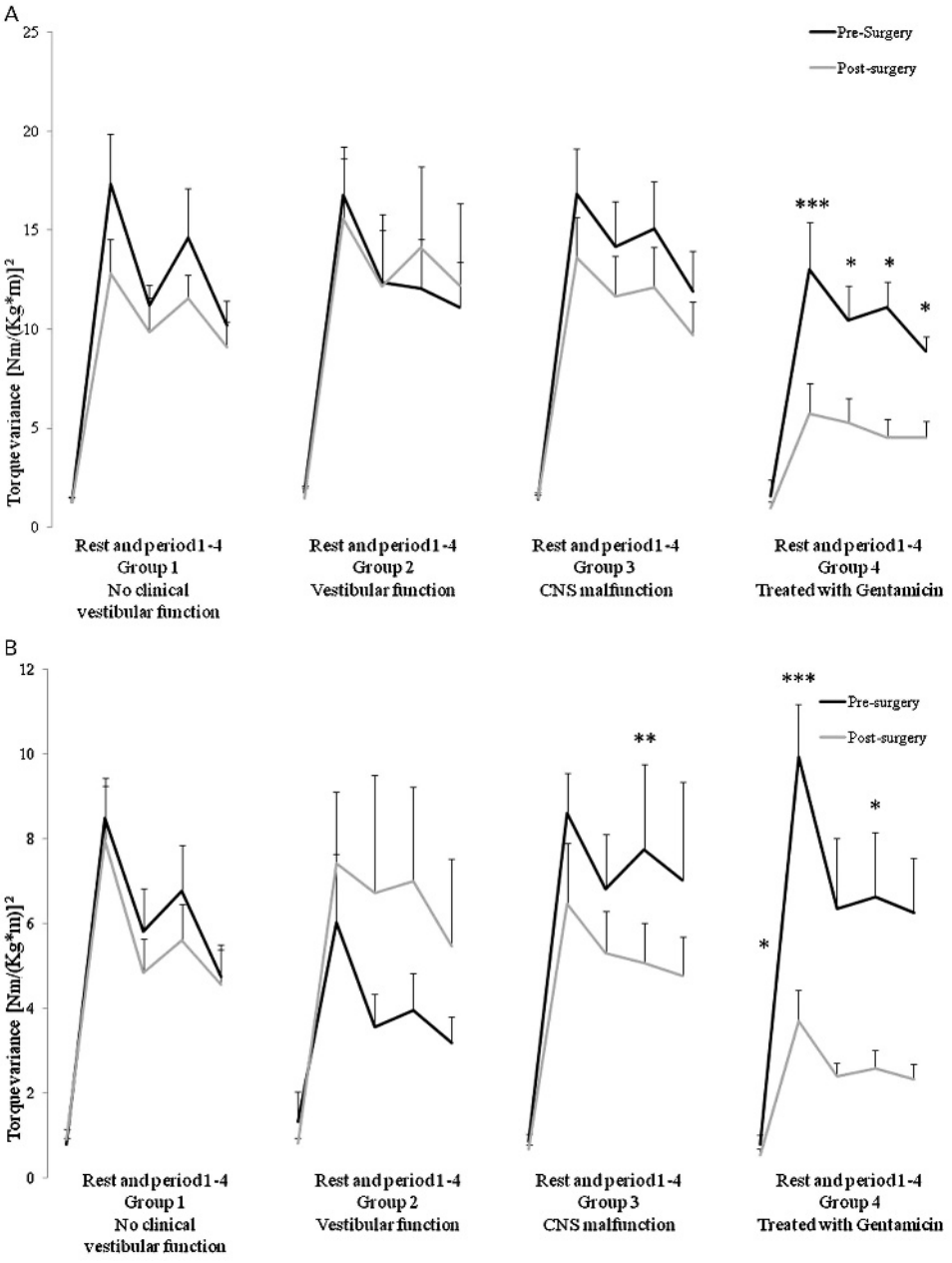

Figure 3 Normalised anteroposterior torque variance in all groups, closed eyes (A) and open eyes (B), at the time of primary assessment (black line) and at the follow-up after 6 months (grey line). CNS, central nervous system.

($p<0.05$). Group 2 had significantly more sway with eyes closed in period 1 ($p<0.05$). Group 3 had significantly more sway with eyes closed in period 1 ($p<0.05$) and period 3 ($p<0.01$).

The individual posturography recordings for group 4 are presented in fig 4. For most patients, the induced torque variance increased on the test following gentamicin therapy in the eyes-closed condition. Only for patient 6 did the induced torque variance decrease on the test immediately after gentamicin installation. With the eyes open, there was a stronger tendency for the induced torque variance to decrease with each test, although not uniformly so (patients 3 and 4).

DISCUSSION

Measuring torque variance during vibratory perturbation gives an appreciation of the energy that is spent on maintaining postural control while resolving a sensory conflict.[21] As energy conservation is a fundamental principle, it would seem plausible that a task is handled with more ease if less energy is spent. The results in this study clearly demonstrate that patients pretreated with gentamicin needed or spent less energy at the vibratory posturography test at the time of follow-up. Previous evaluations of vestibular compensation after deafferentation with posturography demonstrate that the performance deteriorates immediately after surgery and improves after 3 months to levels even better than before surgery.[22] This could be argued to be due to learning to handle the postural test itself and not necessarily development of more efficient postural strategies due to sensory reweighting.[12] It has also been argued that the postural disturbances that patients with vestibular deficits experience are not related to the deafferentation itself but rather to the loss of the vestibular role as an orientational and internal reference to other conflicting sensory input.[23] It is conceivable that adaptation processes, essential for coping with the altered sensory information and also in resolving arising sensory conflicts, are impeded by performing both deafferentation and major surgery at the same time. The vestibular training before

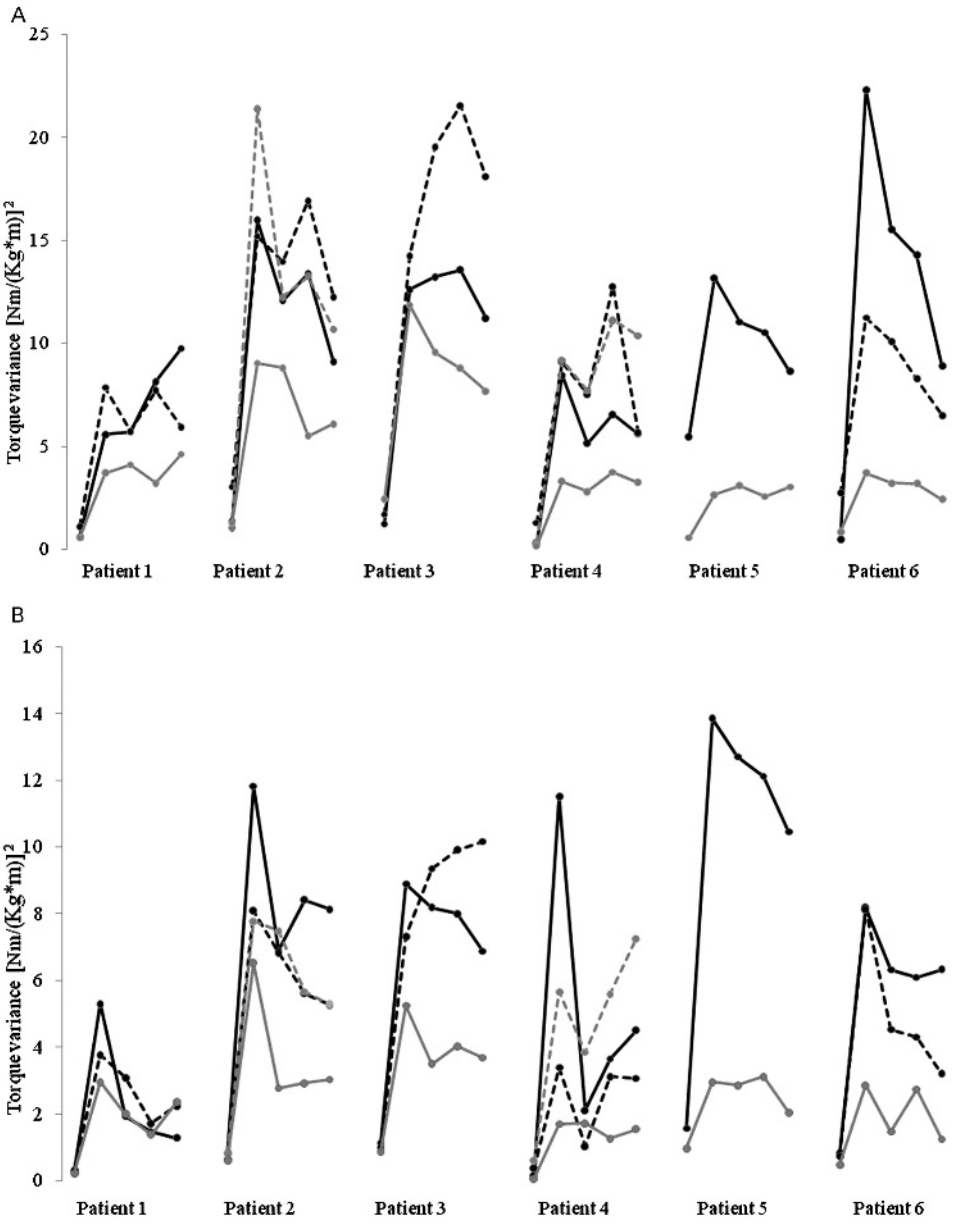

Figure 4 Individual posturography recordings in the gentamicin group as further defined in table 1. The data consist of normalised anteroposterior torque variance. For detailed information as to the timing of the posturography recordings in each individual, see table 1. Black lines, before surgery; dashed black lines, after gentamicin; dashed grey line, after surgery; grey lines, at the follow-up 6 months after surgery.

surgery (PREHAB) is aimed at initiating motor learning at a cellular level before the actual lesion,[18] in line with multiple plasticity mechanisms active in cerebellar and hippocampal adaptation.[13 24] Performing vestibular "PREHAB" simultaneously with the gradual loss of the remaining vestibular function induced by gentamicin treatment[18] enabled patients in group 4 to continuously compensate and adapt.[25] It has been shown that even minor surgery interferes with hippocampal function in aged rodents,[15] and postoperative cognitive function and memory function in particular are impaired, especially in older people.[26 27] Furthermore, the loss of vestibular input affects hippocampal function and integrity,[4] though that effect is greater in the case of bilateral deafferentation.[28] It is thus not improbable that the surgical trauma associated with translabyrinthine surgery would have similar effects on the CNS, delaying central neural adaptive processing.

It is possible to adapt and form long-term memory from the posturography test itself as described by Tjernstrom *et al*.[12] It is also possible that the vestibular training (PREHAB) before surgery was more rigid in the gentamicin group, as they were given a specific time to start the exercises, and that the consultations at the time for gentamicin injections as well as the follow-up may have induced a better compliance as well as a longer period of executing the exercises. However, both these explanations would assume a consecutive improvement on each posturography,[12] which does not seem to occur. It seems therefore more likely that the difference between the groups is the separation in time between sensory deafferentation and surgery.

It is interesting to note the high torque variance with eyes open generated in patients with remaining vestibular function, not treated with gentamicin, at the follow-up. In these patients, the vestibular prehabituation could have been counterproductive, in the sense that the exercises, which mainly train the vestibulo-ocular reflex, are conducted in a sensory setting that will change at the time of surgery.

The patients regarded as clinically deafferent before surgery (group 1) differed from the patients treated with gentamicin. This could be due to a better compliance with exercises in the

gentamicin group but also due to a remaining (although hypoactive) vestibular function in the patients included in group 1. Following the above reasoning, this could yield a counterproductive sensory training.

The patients showing signs of central disorder before surgery (group 3) had a tendency to decrease their torque variance to the follow-up. Although it is difficult to draw any hard conclusions from the data produced by group 3, given the heterogeneity with regards to both remaining vestibular function and the nature of central nervous malfunction, the data suggest that the adaptation processes were not impeded by any central nervous dysfunction. This could be ascribed to the fact that the pressure effects on the cerebellum and brain-stem from the tumour were alleviated at surgery.

Although the number of patients (six) is small, the results indicate that pretreating patients who have a remaining vestibular function with gentamicin before ablative surgery is of benefit not only for postoperative well-being as previously described, but also for long-term learning to withstand perturbed postural control, that is coping with sensory conflicts. Even if the present study is reasonably thorough in assessing the actual vestibular function before surgery, it is nevertheless conceivable that remnants of vestibular function exist though not detected. This perspective indicates a rationale for treating even more patients scheduled for vestibular schwannoma surgery with vestibular PREHAB and gentamicin, at least when no hearing conservation is required. To corroborate such a conclusion however, prospective studies are needed.

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