

# Audiometric Abnormalities in Children with Gaucher Disease Type 3

Doris-Eva Bamiou<sup>1</sup>, Pauline Campbell<sup>1</sup>, Alki Liasis<sup>2</sup>, J. Page<sup>1</sup>, T. Sirimanna<sup>1</sup>, S. Boyd<sup>2</sup>, A. Vellodi<sup>3</sup>, C. Harris<sup>4</sup>

<sup>1</sup>Department of Audiological Medicine, Great Ormond Street Hospital for Children, London, UK

<sup>2</sup>Department of Clinical Neurophysiology, Great Ormond Street Hospital for Children, London, UK

<sup>3</sup>Metabolic Medicine Unit, Great Ormond Street Hospital for Children, London, UK

<sup>4</sup>Department of Ophthalmology, Great Ormond Street Hospital for Children, London, UK

Exogenous enzyme replacement therapy achieves satisfactory biomedical correction in Gaucher type 1 disease and may halt or reverse neurological progression in type 3, while it does not appear to influence the outcome in type 2. In view of the therapeutic possibilities, early detection and monitoring of type 3 Gaucher disease, as well as evaluation of the effectiveness of enzyme therapy on neuronopathic involvement is necessary. The objective of this study was to evaluate the extent of brainstem disease in children with proven Gaucher type 3, by means of an audiological test battery. We studied 9 patients with Gaucher type 3 disease. The tests included baseline audiometric tests, as well as auditory brainstem evoked responses (ABR), acoustic reflexes and medial olivo-cochlear suppression by contralateral noise tests, that involve overlapping but not identical efferent and afferent pathways and brainstem structures. We found a constellation of abnormalities including bilaterally raised acoustic reflexes, poor medial olivo-cochlear suppression, and very poor brainstem evoked potentials. These abnormalities could be due to a single lesion in the dorsomedial brainstem, or to multiple lesions, and further study is needed to clarify this issue. Combined audiological tests may provide information on the severity of the neurological involvement and should therefore be part of a standard assessment for the diagnosis as well as for long term neurological monitoring of Gaucher type 3 patients.

**Key words:** Auditory brainstem – Evoked potentials – Acoustic reflex – Gaucher's disease

## Abbreviations

ABR	auditory brainstem evoked response
ART	acoustic reflexes thresholds
ERT	enzyme replacement therapy
GD	Gaucher disease
MOCS	middle olivo-cochlear suppression by contralateral noise
OAE	otoacoustic emissions
PTA	pure tone audiogram
SIF	saccade initiation failure

SOC	superior olivary complex
TB	trapezoid body
TEOAE	transient otoacoustic emissions
VCN	ventral cochlear nucleus

## Introduction

Gaucher disease (GD) is the most common lysosomal storage disorder [23]. GD is autosomal recessive and characterised by insufficiency of the enzyme glucocerebrosidase, which results in accumulation of glucosylceramide within macrophages affecting spleen, liver, and bones [28] as well as the central nervous system in some patients [10,11]. Thus, GD is classified into 3 clinical subtypes. In type 1 GD (non-neuronopathic GD) there are only systemic manifestations with no primary neurological problems. In type 2 GD, there is an early onset of systemic and rapidly progressive primary neurological brainstem degeneration leading to death usually in the first two years. Type 3 Gaucher disease is often associated with severe systemic disease with an onset in early infancy. Neurological progression is slower than in type 2 and variable. Neurological features may include ataxia, myoclonus, seizures, and dementia [1,9].

Exogenous enzyme replacement therapy (ERT) has replaced bone marrow transplant (BMT) as the treatment of choice for GD1, and in most cases satisfactory biomedical correction can be achieved [13]. The effect of ERT on neuronopathic GD is less clear. In type 2 neurological progression is unremitting in spite of large doses of ERT [19]. In type 3 high dose rates may halt or even reverse neurological progression although the outcome is not always so favourable [2,33]. In view of the therapeutic possibilities, there is a need for tests that will enable early detection, monitoring and evaluation of therapy effectiveness [13] in type 3 Gaucher disease.

At present, the diagnosis of type 3 disease is based on clinical grounds [14] and may not be made until severe irreversible neurological signs have appeared. An early sign of neuronopathic disease is a disturbance of eye movement characterised

Case	Age (years)	Gender	Neurology	Genotype	Treatment
1	4.2	m	SIF, epilepsy	L444 P/L444 P	ERT
2	10.3	f	SIF, ataxia	L444 P/L444 P	BMT
3	4.7	f	SIF	L444 P/L444 P	ERT
4	3.3	f	SIF	L444 P/L444 P	ERT
5	4.5	f	SIF	L444 P/L444 P	ERT
6	5.5	f	SIF	L444 P/L444 P	ERT
7	11.7	f	SIF	L444 P/L444 P	ERT
8	14.5	f	SIF	L444 P/L444 P	BMT (2)
9	11.0	f	SIF	Pending	ERT

Abbreviations: BMT = bone marrow transplant, ERT = Enzyme replacement therapy, f=female, m=male, SIF = Saccade initiation failure

**Table 1** Summary of the clinical characteristics of the Gaucher type 3 subjects

by a reduced ability to trigger saccades (saccade initiation failure, ocular motor apraxia) and reduced speed of saccades, that may both be attributed to brainstem lesions [14] in view of post mortem findings [7,19]. These abnormalities are probably diagnostic of type 3 disease after enzymatic diagnosis of GD has been made, but they do not predict neurological severity or rate of progression [29]. Another sign of neuronopathic disease is the detection of abnormal auditory brainstem evoked potentials (ABR), reported in both GD2 [18,19,22] and GD3 [33]. However, the ABR may indicate a brainstem abnormality, but there is no precise correspondence between the ABR waveform and anatomical lesion sites [16], while the interpretation of the ABR depends on peripheral hearing parameters, but audiometric thresholds in neuronopathic GD have not been reported. Audiologic detection and evaluation of brainstem disorders requires a multiple test strategy [17]. Acoustic reflex threshold measurement (ART) [6] and otoacoustic emission suppression by contralateral noise (MOCS) [30] are two objective tests, i.e., that do not rely on the patient's response, that have been used for evaluation of brainstem lesions. The combination of ABR with ART provides patterns of abnormality that may differentiate between lesions affecting the brainstem, the auditory nerve or the cochlea [6]. Otoacoustic emission middle olivo-cochlear bundle suppression by contralateral noise (MOCS) is reduced or absent in patients with intrinsic brainstem lesions and the site and size of the lesion determines whether the suppression is affected unilaterally or bilaterally [30].

The objective of this study was to evaluate the extent and level of brainstem disease in children with proven GD3 by means of an audiological test battery. We used for this purpose baseline audiometric tests as well as auditory brainstem evoked responses, acoustic reflexes and medial olivo-cochlear suppression by contralateral noise tests, as these three responses involve overlapping but not identical efferent and afferent pathways and brainstem structures.

## Subjects and Methods

### Subjects

Eleven patients with type 3 Gaucher disease who were attending the Metabolic Unit at Great Ormond Street Hospital were investigated. Diagnosis of Gaucher disease had been previously made by demonstration of deficient glucosidase activity either in peripheral leucocytes or fibroblasts. The diagnosis of

type 3 (neuronopathic) Gaucher disease was based upon the finding of saccade initiation failure (SIF) on bi-temporal direct current electro-oculography and simultaneous video, described in detail elsewhere [14]. The presence of otitis media with effusion causing conductive type hearing loss ("glue ear") as assessed by abnormal audiometric and impedance audiometry tests was a criterion of exclusion from the study and two subjects were thus excluded from further analysis.

The age range of the remaining 9 patients that were included in this study ranged between 3.3 to 14.5 years at the time of the study, with 8 female and 1 male patient. Table 1 summarises the clinical features of each of the patients. In view of the group's age range as well as of different treatment parameters, no attempt was made to rank the clinical severity of the disease; however, having taken into consideration age and treatment, the most severely neurologically affected patient appeared to be Case 1, as he had epilepsy in addition to saccade initiation failure. An equal number of normal age-matched children with normal peripheral hearing on baseline audiometric procedures were used as controls. Ethical Committee approval and informed consent from each subject were obtained.

### Methods

All patients underwent a clinical interview to obtain relevant information and otoscopy to exclude visual evidence of ear disease. Baseline audiometric results were obtained prior to and in the same session with the brainstem tests.

#### I. Baseline audiometric tests

**Pure-tone audiometry** was carried out using a GSI 61 audiometer with TDH-49 earphones in a sound-proof room. Air-conduction thresholds were measured for each ear at 0.25, 0.5, 1, 2, 4, and 8 kHz, following the procedure recommended by the British Society of Audiology [3]. Hearing was considered normal when thresholds were better than 20 dB HL in all frequencies in both ears.

**Acoustic impedance tests:** Tympanometry was obtained with a probe signal continuous 226 Hz tone at 85 dB SPL using a GSI-33 Middle Ear Analyser. Tympanograms were considered normal if middle ear pressure was  $> -150$  mm H<sub>2</sub>O and compliance was  $> 0.3$  ml.

**Otoacoustic emissions (OAEs):** The presence of otoacoustic emissions indicates that the preneural cochlear receptor, as well as the middle ear mechanism, give a normal response to sound [20]. Transient otoacoustic emissions (TEOAE) tests evoke emissions from a large part of the cochlea, providing information over a wide frequency range. Otoacoustic emissions tests were carried out using the ILO88/92 Otodynamic Analyser. We used a standard default set-up, as described by Kemp et al [20], and the data considered were TEOAE response level, noise level (dB SPL) and reproducibility. Briefly, a probe containing a transducer and microphone was inserted into the external auditory meatus and was used to present stimuli and record emissions. During the initial insertion of the probe (pre-collection mode), a series of stimuli were presented, and the stimulus spectrum was derived. The emission data of this study were obtained using the preset mode with a low-cut filter and a stimulus band width of 500 to 5000 Hz. The stimulus intensity across ears ranges from 80 to 86 dB peak SPL with 50 clicks per second. The ILO92 (Otodynamics) system was set in non-linear click mode, in which responses to sets of four clicks are subaveraged and alternately sent to two different buffers. After 260 subaverages were collected on each buffer, the test was complete and was stopped automatically [20]. The presence of normal OAEs in the 2.5 to 20 msec post stimulus period was determined by overall response amplitude signal to noise ratio of at least 3 dB and waveform reproducibility in at least three octave bands of > 75% [15].

## II. Brainstem tests

**Acoustic reflexes:** The acoustic reflex arc is a four-synaptic neural chain, consisting of the 8th N, the cochlear nucleus, superior olivary complex and the ipsi- and contralateral medial facial nerve motoneurons [6]. For the ipsilateral reflex, the 7th nucleus receives most of its input directly from ventral cochlear nucleus (VCN) via the trapezoid body (TB). However, some fibres from the VCN are relayed to the 7th nucleus via the ipsilateral superior olivary complex (SOC). For the contralateral reflex, the 7th nucleus receives afferents from the contralateral VCN via the contralateral SOC [36]. Acoustic reflex thresholds have a 70% sensitivity in identifying brainstem lesions [6].

*Acoustic reflex threshold (ART)* measurements were obtained by stimulating each ear at 0.5, 1, 2 and 4 kHz, at levels ranging from 70 up to a maximum output of 120 dB HL, in 5 dB steps, for contralateral and ipsilateral stimulation. A consistent change in compliance of  $\geq 0.03$  ml following stimulation, is a criterion for the presence of the acoustic reflex. Acoustic reflexes were considered as abnormal if they exceeded 105 dBnHL at two or more adjacent frequencies or if the interaural threshold difference exceeded 10 dB on at least two adjacent frequencies [6]. The patterns interpreted as indicating brainstem lesion were the vertical (abnormal ART by stimulation of one ear only), horizontal (ART abnormal by contralateral stimulation of both ears), inverted L (combined vertical and horizontal) and full house (all ipsilateral and contralateral reflexes abnormal) [6].

**Medial olivo-cochlear suppression test (MOCS):** Contralateral acoustic stimulation reduces the amplitude and shifts the phase of click-evoked otoacoustic emissions [32]. This effect is mediated by a neural pathway consisting of afferent fibres

from the cochlea to the superior olivary complex and of efferent fibres from the superior olivary complex (SOC) via the medial olivo-cochlear bundle to the other cochlea [21]. The pathway involves the projection from olivo-cochlear neurons mostly in the medial region of the superior olivary complex (SOC) to the contralateral cochlea. MOCS tests the reduction in the TEOAE due to noise stimulation of the contralateral ear, thus testing the integrity of the efferent contralateral olivo-cochlear system [4]. The medial olivo-cochlear suppression test consisted of transient otoacoustic emissions recording with and without contralateral ear noise stimulation, the difference in responses being considered to be due, at least in part, to the medial olivo-cochlear bundle (MOCB) effect [4]. A dual channel OAE analyser was used (channel A for ipsilateral and channel B for contralateral stimulation) with a linear click at  $60 \pm 3$  dB SPL intrameatal peak stimulus level ipsilateral stimulus and a 5 ms burst of white noise (0.5–6 kHz) at 40 dB SL contralateral stimulus. A total of 600 sweeps in 10 groups of 60 sweeps were recorded by using an alternating technique, "Difference B on/off" mode, from the ILO92 software. The difference obtained by subtraction of the average responses (response without noise minus response with noise) represented the suppression effect. Suppression was considered as abnormal if less than 1 dB [4].

**Auditory brainstem evoked responses (ABR):** ABR were recorded with the Nicolet Spirit equipment. Electrodes were placed at the vertex (Cz) and on each mastoid (A2 and A3), the non-test mastoid being used as ground. Monaural click stimuli alternating in polarity (100  $\mu$ s) were presented at a rate of 11.1 per second via TDH-49 headphones. Electrode impedance was less than 5 K ohms. The electrical activity was amplified and filtered (150–3000 Hz). A total of 1024 responses were given for each average. The filter settings were 150–3000 Hz, (12 dB per octave roll-off) with an averaging window of 20 ms and an artifact-rejection feature set at 25 V peak to peak. The collected waveforms were processed and stored on disc for off-line analysis. A standard minimum intensity of 90 dBnHL was used provided that clear waveforms with distinct waves I, III, and V were observed. The analysis was restricted to waves I, III and V. We assessed waveform morphology, peak latency and interwave latency, as defined by Schwartz et al [34]. A response was classified as abnormal if the waveforms were non-repeatable or absent, or if the wave or inter-wave peak latencies were outside the mean by more than 2 SD, using our own laboratory's normative data (Campbell, unpublished). Despite the lack of one to one correlation between the ABR waveforms and distinct anatomical structures [16], we interpreted the ABR abnormalities according to Möller's classification of ABR neural generators [25], with peak I corresponding to the distal portion of the VIIIth nerve, peak III mainly corresponding to the superior olivary complex and wave V corresponding to the termination of the inferior colliculus and to the lateral lemniscus.

## Statistical analysis

All data were analysed using the Statistical Package for the Social Sciences (SPSS).

**Table 2** Summary of audiometric results

	PTA	TYMP	TEOAE	ART	MOCS	ABR
1	normal	normal	normal	not tested	not tested	abnormal
2	normal	normal	normal	abnormal	abnormal	abnormal
3	normal	normal	normal	abnormal	abnormal	abnormal
4	normal	normal	normal	abnormal	normal	normal
5	normal	normal	normal	abnormal	abnormal	abnormal
6	normal	normal	normal	abnormal	normal	normal
7	normal	normal	normal	abnormal	abnormal	abnormal
8	normal	normal	normal	abnormal	abnormal	abnormal
9	normal	normal	normal	abnormal	abnormal	normal

Abbreviations: ABR= auditory brainstem responses, ART = acoustic reflex thresholds, MOCS = medial olivo-cochlear suppression by contralateral noise test, PTA = Pure tone audiometry, TEOAE = Transient evoked otoacoustic emissions, TYMP = Tympanometry

**Table 3** Summary of ABR abnormalities of subjects at 90 and 100 dBnHL

Case	ABR (90 dBnHL)		ABR (100 dBnHL)	
	Right	Left	Right	Left
1	absent I–V	absent I–V	absent II–V	absent II–V
2	absent II–V	absent V; delayed III, I–III	delayed V; delayed IWI	delayed V; delayed IWI
3	delayed III, V; delayed IWI	delayed III, V; delayed IWI	delayed V; delayed IWI	delayed V; delayed IWI
4	WNL	WNL	not tested	not tested
5	delayed V; delayed I–V	WNL	WNL	WNL
6	WNL	WNL	not tested	not tested
7	absent V	absent V	absent V	WNL
8	absent II–V	absent II–V	delayed III, V; delayed IWI	delayed III, V; delayed IWI
9	WNL	WNL	WNL	WNL

Abbreviations: IWI = interwave intervals, WNL = within normal limits

## Results

### I. Baseline audiometric tests

All 9 subjects had normal audiograms and single frequency tympanometry. TEOAEs were normal in all 9 subjects. The mean TEOAE amplitudes were significantly reduced ( $t = 2.89$ ,  $p = 0.01$ ) in all Gaucher patients ( $12.5 \pm 7.2$  dB right ear;  $13.4 \pm 5.7$  dB left ear) compared with control subjects ( $18.8 \pm 4.8$  dB right ear;  $16.9 \pm 5.3$  dB left ear).

### II. Brainstem tests

**Acoustic reflexes:** The acoustic reflex response was measured in 8 of 9 patients. In one case, acoustic reflex thresholds could not be obtained due to the patient's oversensitivity to the acoustic stimuli. The ART was abnormal in all of the 8 cases measured. In 6/8 cases, all ipsilateral and contralateral reflexes were elevated or absent across three adjacent frequencies ("full-house" pattern). 2 cases had "inverted L" pattern, i.e., abnormal ipsilateral ART on one ear and abnormal contralateral ART on both ears. Both these abnormalities are reported to correspond with intra-axial brainstem lesions [6].

**Medial olivo-cochlear suppression test:** All age-matched controls had normal suppression. 8 subjects were evaluated using MOCS test (Table 2). We were unable to record MOCS in

Case 1 because the subject was unable to report 40 dB SL required to complete the test. Suppression was normal in 2 out of 8 (25%) subjects and reduced or absent in 6 (75%) (Table 2). In addition, medial olivo-cochlear suppression was significantly reduced in Gaucher patients compared to controls ( $t = 5.92$ ,  $p = 0.00$ ).

**Auditory brainstem evoked potentials:** At a stimulus intensity of 90 dBnHL, the ABR was normal in 3 children (Cases 4, 6, 9) and abnormal in 6. Wave I was identifiable in 8 out of 9 cases (16 out of 18 ears). Wave III was absent in a total of 5 ears and delayed in 3. Wave V was absent in 9 ears and delayed in 3 (Table 3). Table 3 describes in detail the abnormalities in each case.

Because of the apparent poor morphology, the ABR was recorded at a higher intensity of 100 dBnHL in 7 cases. In the remaining two cases, the ABR could not be obtained due to the patients' oversensitivity to the acoustic stimuli at 100 dBnHL. With an increased stimulus intensity of 100 dBnHL, wave III was absent in 2 ears and delayed in 2. Wave V was absent in 3 ears and delayed in 6 (Table 3).

## Discussion

This is the first study of Gaucher disease type 3 to use a battery of audiometric tests in order to evaluate the extent and site of involvement of the auditory pathway including the brainstem. Previous studies have only employed ABR for this purpose [19,22,33]. We investigated 11 patients who had been diagnosed enzymatically with Gaucher disease and in whom the diagnosis of neuronopathic disease had been established by the finding of saccade initiation failure ("ocular motor apraxia") and slow saccades on objective recordings of saccade eye movements [14,29].

Our 9 subjects had normal pure tone audiogram thresholds. Individual OAEs were within normal limits but the OAE amplitude mean was significantly below that of age-matched controls, although equivalent to the OAE amplitude reported by other investigators for this age-range and OAE protocol [12,31]. It is difficult to decide whether this finding indicates subclinical outer hair cell pathology, as up to 30% of the OHC population may be damaged before there is any audiometric evidence in the pure tone audiometry [5]. Similar subtle deficits have been reported in insulin-dependent diabetes mellitus [8]. It is unclear whether this subtle deficit, if indeed present, is due to the disease process or to other morbidity associated with the disease.

The combination of abnormal ABR with abnormalities in the other two brainstem tests as well as the presence of saccade initiation failure provided further evidence on the extent of brainstem involvement. Ipsilateral and contralateral acoustic (stapedial) reflex thresholds were abnormal in all 8 tested cases, with 6 cases of "full house" and 2 case of "inverted L" pattern. The presence of both ipsi- and contralateral abnormalities, i.e., "full-house", in the presence of normal middle/inner ear function usually indicates central disease that can be localised to the cochlear nuclei and the olivary nuclei with a sensitivity of 75% [6]. Alternatively, raised reflexes could reflect bilateral involvement of the facial nucleus or its fascicle that proceeds dorsomedially, bends around the 6th nucleus and returns ventrolaterally to exit the brainstem. A midline lesion near the genu could thus affect both fascicles as well as the horizontal saccade centres in the PPRF. Interestingly, 6th nerve palsies have been reported in type 3 disease [14].

The medial olivo-cochlear suppression mediated by the efferent contralateral olivo-cochlear system [4] was bilaterally abnormal in 6 out of 8 patients tested. As the crossing olivo-cochlear axons pass the midline in the dorsal brainstem under the genu of the facial nerve [35], it is plausible that lesions affecting the horizontal saccades could also compromise contralateral suppression. MOCS was normal in two of our youngest patients, who also had better ABR than the rest (normal in one and absent wave V in one case).

The commonest finding in the ABR was absent or delayed wave V in 12 out of 18 ears (66%), followed by an absent or delayed wave III in 8 out of 18 ears (44%). Wave III is thought to be generated by the cochlear nucleus, and wave V by the lateral lemniscus and/or the contralateral inferior colliculus [25]. The sensitivity of ABR in identifying intra-axial brainstem lesions can be as high as 97% [27]. Therefore, the abnormal ABR in our patients may indicate intra-axial lower brainstem involve-

ment, from the level of the cochlear nucleus and upwards. Five cases had abnormal results in all three brainstem tests. Case 1, who had the most severe neurological involvement, had the worse ABR findings of the group. Cases 5 and 7 had milder abnormalities in the ABR, with intact wave III, indicating that the cochlear nucleus was not affected or was only mildly affected by the lesion while the finding of abnormal ABR wave V and bilaterally abnormal ART and MOCS could indicate pathology involving the SOC and higher auditory pathway as well as the VIII nerve nuclei. Cases 2, 8, 7 had more severe involvement than the previous two cases, with delayed or absent ABR wave III and bilaterally abnormal MOCS and ART, possibly due to severe neurological involvement at the level of the cochlear nucleus [26]. This is consistent with post mortem histopathology reports in type 2 GD with similar ABR findings [19,22]. Interestingly, increased stimulus level (100 dBnHL) elicited delayed ABR waveforms in Cases 2 and 7, as has also been reported in Gaucher type II [22], but not in Case 8, which may again indicate more severe involvement of the latter than the former two cases. We also observed that the children who had started the ERT before their second birthday tended to have milder overall audiometric abnormalities than children who had started ERT later on or who had had a bone marrow transplant. However, as the children with early onset ERT were also younger than the rest, it is difficult to assess whether the lesser impairment is due to age differences and stage of the disease or to treatment parameters and a prospective study would be more appropriate to address these issues.

In summary, this is the first extensive study of auditory pathways in children with Gaucher type 3 disease. We have found a constellation of abnormalities including raised acoustic reflexes, poor medial olivo-cochlear suppression, and very poor brainstem evoked potentials. While it is possible that some of these abnormalities could be consistent with a single lesion in the dorsomedial brainstem in and around the saccadic eye movement centres, it is more likely that there are additional lesions. Further study is needed to clarify the origins of these abnormalities. The results of this cross-sectional study indicate that combined audiological tests may provide information on the severity of the neurological involvement in Gaucher type III. We are currently undertaking detailed audiological evaluation in addition to eye movement studies as standard assessment in our Gaucher type 3 patients on a prospective basis in order to assess whether serial audiological evaluation may serve for long term monitoring of any neurological progression.

## References

- 1 Beutler E, Grabowski GA. Gaucher disease. In: Scriver CR, Beaudet AL, Sly WS et al (eds). *The Metabolic and Molecular Basis of Inherited Disease*, 6th ed. New York: McGraw-Hill, 1995: 2641–2670
- 2 Bosman DK, Hollak CE, Aerts JM, Bakker HD. The effect of enzyme therapy in a patient with Gaucher disease type III. *Journal of Inherited Metabolic Medicine* 1996; 19: 703–704
- 3 British Society of Audiology. Recommended procedure for pure tone audiometry using a manually operated instrument. *Br J Audiol* 1981; 15: 213–216
- 4 Ceranic BC, Prasher DK, Raglan E, Luxon LM. Tinnitus after head injury: evidence from otoacoustic emissions. *Journal of Neurology, Neurosurgery and Psychiatry* 1998; 65: 523–529

- <sup>5</sup> Clark WW, Bohne BA. Effects of noise on hearing. *JAMA* 1999; 281: 1658 – 1659
- <sup>6</sup> Cohen M, Prasher. ABR and ART in neuro-otological diagnosis. *Scandinavian Audiology* 1988; 17: 153 – 162
- <sup>7</sup> Conradi NG, Sourander P, Nilsson O, Svennerholm L, Erikson A. Neuropathology of the Norrbottnian type of Gaucher disease, morphological and biochemical studies. *Acta Neuropathol* 1984; 65: 99 – 109
- <sup>8</sup> Di Leo MA, Di Nardo W, Cercone S, Ciervo A, Lo Monaco M, Greco AV, Paludetti G, Ghirlanda G. Cochlear dysfunction in IDDM patients with subclinical peripheral neuropathy. *Diabetes Care* 1997; 20: 824 – 828
- <sup>9</sup> Dreborg S, Erikson A, Hagberg B. Gaucher disease – Norrbottnian type I: General clinical description. *Eur J Pediatr* 1980; 133: 107 – 118
- <sup>10</sup> Erikson A. Gaucher disease – Norrbottnian type (III). Neuropediatric and neurobiological aspects of clinical patterns and treatment. *Acta Paediatr Scandinavica – Supplement* 1986; 326: 1 – 42
- <sup>11</sup> Erikson A, Bembi B, Schiffman R. Neuronopathic forms of Gaucher's disease. *Bailliere's Clinical Haematology* 1997; 10: 711 – 723
- <sup>12</sup> Glattke TJ, Pafitis IA, Cumiskey C, Herer GR. Identification of hearing loss in children using measures of transient otoacoustic emission reproducibility. *Am J Audiol* 1995; 4: 71 – 86
- <sup>13</sup> Grabowski GA, Leslie N, Wenstrup R. Enzyme therapy for Gaucher disease: the first 5 years. *Blood Reviews* 1998; 12: 115 – 133
- <sup>14</sup> Harris CM, Taylor DSI, Vellodi A. Ocular motor abnormalities in Gaucher disease. *Neuropediatrics* 2000; 30: 289 – 293
- <sup>15</sup> Hurley RM, Musiek FE. Effectiveness of transient-evoked otoacoustic emissions (TEOAEs) in predicting hearing level. *Journal of the American Academy of Audiology* 1994; 5: 195 – 203
- <sup>16</sup> Jacobson GP, Jacobson JT, Ramadan N, Hyde M. Auditory brainstem response measures in acoustic nerve and brainstem disease. In: Jacobson JT (ed). *Principles and Applications in Auditory Evoked Potentials*. London: Allyn and Bacon; 1994: chapter 16
- <sup>17</sup> Jerger J, Neely J, Jerger S. Speech, impedance and auditory brainstem response audiometry in brainstem tumours. *Arch Otolaryngol* 1980; 106: 218 – 223
- <sup>18</sup> Kaga K, Azuma C, Imamura T, Murakami T. Auditory brainstem response (ABR) in infantile Gaucher's disease. *Neuropediatrics* 1982; 13: 207 – 210
- <sup>19</sup> Kaga K, Ono M, Yakumaru K, Owada M, Mizutani T. Brainstem pathology of infantile Gaucher's disease with only wave I and II of auditory brainstem response. *J Laryngol Otol* 1998; 112: 1069 – 1073
- <sup>20</sup> Kemp DT, Ryan S, Bray P. A guide to the effective use of otoacoustic emissions. *Ear and Hearing* 1990; 11: 93 – 105
- <sup>21</sup> Klinke R, Galley N. Efferent innervation of vestibular and auditory receptors. *Physiological Reviews* 1984; 54: 316 – 357
- <sup>22</sup> Lacey DJ, Terplan K. Correlating auditory evoked and brainstem histologic abnormalities in infantile Gaucher disease. *Neurology* 1984; 34: 539 – 541
- <sup>23</sup> Meikle J P, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. *JAMA* 1999; 281: 249 – 254
- <sup>24</sup> Möller AR. Physiology of the ascending auditory pathway with special reference to the auditory brainstem response (ABR). In: Pinheiro ML, Musiek FE (eds). *Assessment of Central Auditory Dysfunction: Foundations and Clinical Correlates*. Baltimore: Williams and Wilkins, 1985: 23 – 41
- <sup>25</sup> Möller AR. Neural generators of auditory evoked potentials. *Seminars in Hearing* 1994; 19: 11 – 27
- <sup>26</sup> Möller AR, Janetta PJ, Möller MB. Neural generators of brainstem evoked potentials. Results from human intracranial recordings. *Ann Otol* 1981; 90: 591 – 596
- <sup>27</sup> Musiek F, Baran J. Assessment of the human central auditory nervous system. In: Altschler R, Bobbin R, Clopton B, Hoffman D (eds). *Neurobiology of Hearing: The Central Auditory System*. New York: Raven Press, 1991: 411 – 437
- <sup>28</sup> Pastores GM. Gaucher's Disease. Pathological features. *Bailliere's Clinical Haematology* 1997; 10: 739 – 749
- <sup>29</sup> Patterson MC, Horowitz M, Abel RB, Currie JN, Yu K-T, Kaneski C, Higgins JJ, O'Neil RR, Fedio P, Pikus A, Brady RO, Barton NW. Isolated supranuclear gaze palsy as a marker of severe systemic involvement in Gaucher's disease. *Neurology* 1993; 43: 1993 – 1997
- <sup>30</sup> Prasher D, Ryan S, Luxon L. Contralateral suppression of transiently evoked otoacoustic emissions and neuro-otology. *Br J Audiol* 1994; 28: 247 – 254
- <sup>31</sup> Prieve BA, Fitzgerald TS, Schulte LE. Basic characteristics of click-evoked otoacoustic emissions in infants and children. *Journal of the Acoustical Society of America* 1997; 102: 2860 – 2870
- <sup>32</sup> Ryan S, Kemp DT, Hinchcliffe R. The influence of contralateral acoustic stimulation on click evoked otoacoustic emissions in humans. *Br J Audiol* 1991; 25: 391 – 397
- <sup>33</sup> Schiffmann R, Heyes MP, Aerts JM, Dambrosia JM, Patterson MC, DeGraba T, Parker CC, Zirzow GC, Oliver K, Tedeschi G, Brady RO, Barton NW et al. Prospective study of neurological responses to treatment with macrophage targeted glucocerebrosidase in patients with type 3 Gaucher disease. *Ann Neurol* 1997; 42: 613 – 621
- <sup>34</sup> Schwartz DM, Morris MD, Jacobson JT. The normal auditory brainstem response and its variants. In: Jacobson JT (ed). *Principles and Applications in Auditory Evoked Potentials*. London: Allyn and Bacon, 1994: chapter 6
- <sup>35</sup> Warr WB. Organization of olivocochlear efferent systems in mammals. In: Webster DB, Popper AN, Fay RR (eds). *The Mammalian Auditory Pathway: Neuroanatomy*. London: Springer-Verlag, 1992: chapter 7
- <sup>36</sup> Webster DB. An overview of mammalian auditory pathways with an emphasis on humans. In: Webster DB, Popper AN, Fay RR (eds). *The Mammalian Auditory Pathway: Neuroanatomy*. Chapter 1. London: Springer-Verlag; 1992

Dr. Doris-Eva Bamiou

Audiology Department  
Great Ormond Street Hospital for Children, NHS Trust  
Great Ormond Street  
London WC1N 3JH  
UK

E-mail: doriseva@ndirect.co.uk