

# An Unusual Case of X-Linked Adrenoleukodystrophy with Auditory Processing Difficulties as the First and Sole Clinical Manifestation

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## Abstract

X-linked adrenoleukodystrophy (X-ALD) is characterized by demyelination that is associated with a deficient beta-oxidation of very long chain fatty acids. We report the unusual case of a male adult with X-ALD who was diagnosed at the age of 26 by a brain MRI performed because his brother had been diagnosed with a rapidly deteriorating form of X-ALD. His sole symptom was hearing difficulties in the presence of a normal audiogram since childhood. He has remained stable for seven years. Central auditory testing in our patient revealed severe deficits in several auditory processes. These findings correlated with involvement of the auditory pathway at the level of the trapezoid body, and posterior corpus callosum in particular, on his brain MRI. This case highlights not only the need for thorough audiological investigation of the patient who complains of hearing difficulties in the presence of a normal audiogram, but also that audiological investigations could be of value in the phenotypic evaluation of cases with adrenoleukodystrophy.

**Key Words:** Adrenoleukodystrophy, auditory processing, brainstem, central auditory disorders, corpus callosum

**Abbreviations:** SOC= superior olivary complex; VCN = ventral cochlear nucleus; X-ALD = X-linked adrenoleukodystrophy

## Sumario

Una adrenoleucodistrofia ligada al cromosoma X (X-ALD) se caracteriza por una desmielinización que se asocia con una oxidación beta deficiente en los ácidos grasos de cadena muy larga. Reportamos el caso inusitado de un adulto con X-ADL, quien fue diagnosticado a la edad de 26 años por un MRI del cerebro, realizado en virtud de que a su hermano se le había diagnosticado una forma de X-ALD de rápido deterioro. Su único síntoma eran dificultades auditivas en presencia de un audiograma normal desde la niñez. Su condición ha permanecido estable por siete años. Las pruebas auditivas centrales en nuestro paciente revelaron deficiencias severas en varios procesos auditivos. Estos hallazgos correlacionaron con el compromiso de la vía auditiva particularmente a nivel del cuerpo trapezoide y del cuerpo ca-

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lloso posterior, en su MRI. Este caso destaca la necesidad no solamente de hacer una investigación audiológica completa en el paciente que se queja de dificultades auditivas en presencia de un audiograma normal, sino también que las investigaciones audiológicas pueden ser de valor en la evaluación fenotípica de casos con adrenoleucodistrofia.

**Palabras Clave:** Adrenoleucodistrofia, procesamiento auditivo, tallo cerebral, trastornos auditivos centrales, cuerpo caloso

**Abreviaturas:** nHL = nivel auditivo normal; SOC = complejo olivar superior; VCN = núcleo coclear ventral; X-ALD = adrenoleucodistrofia ligada al cromosoma X

**X**-linked adrenoleukodystrophy is a demyelinating disease associated with an impairment of beta-oxidation of very long chain fatty acids in peroxisomes. On the basis of the age at onset, sites of clinical involvement, and rate of neurologic deterioration, Moser et al (2001) defined seven phenotypes in affected males, namely the childhood cerebral, adolescent, adrenomyeloneuropathy, adult cerebral, olivopontocerebellar, "Addison only," and asymptomatic forms.

The rapid progression in the childhood cerebral form of ALD is associated with perivascular infiltration of lymphocytes in brain white matter, but the cause of the inflammatory demyelinating reaction is unknown. The loss of myelin is confluent and more pronounced in the parieto-occipital regions, while axons are relatively spared. School difficulties and impaired hearing with difficulty understanding speech in noise, in the presence of a normal audiogram, are amongst the most frequently reported initial symptoms in the childhood cerebral form. Progression is usually rapid, with the patient reaching a vegetative state within 10 years after the neurologic symptom onset (Moser et al, 2001). The prognosis can be estimated on the basis of age and the severity of the brain MRI abnormality (Loes et al 1994), but there are exceptions to these rules, and some patients may remain stable with no

progression of demyelination for up to 12 years after the initial neurologic symptoms (Korenke et al, 1996).

The adult cerebral form is rare. These patients develop symptoms after 21 years of age, with no signs of spinal cord involvement, normal adrenal function in up to 30–50% of patients, and progression to a vegetative state or death three to four years after the onset of symptoms (Moser et al, 2001).

The X-linked adrenoleukodystrophy (X-ALD) gene has been mapped to Xq28 (Migeon et al, 1981) and encodes an ATP-binding cassette transmembrane transporter protein (Mosser et al, 1994). There is no correlation between disease severity and the mutation, and different phenotypes typically occur within the same family (Moser et al, 2001).

We report the unusual case of a male adult with X-ALD, whose sole symptom was hearing difficulties in the presence of a normal audiogram, and in whom central auditory testing revealed auditory processing difficulties that correlated with the abnormal brain MRI.

## CASE HISTORY

**T**he patient first saw a neurologist (PR) at the age of 26 years as his brother had been diagnosed with severe adrenoleukodystrophy. The patient's brother presented with a predominantly psychiatric

disturbance in his early twenties, followed by a progressive motor abnormality that led to him being completely chairbound. He died aged 32. Our patient was diagnosed with X-ALD, on the basis of the family history of X-ALD in his brother, the presence of raised very long chain fatty acids in the plasma, and of characteristic confluent hyperintensity changes in the occipitoparietal regions on his brain MRI. His neurological examination and adrenal function were normal. A cognitive assessment pronounced him of average intelligence, with verbal skills in the low average and nonverbal skills in the upper half of the nonverbal scale. He has been monitored for seven years since diagnosis and has remained stable.

The patient has complained of hearing difficulties since the age of eight years. This complaint led to repeated audiometric assessments. With the exception of one transient episode of otitis media with effusion with mild conductive hearing loss at the age of nine years, there was no history of glue ear, and pure-tone audiograms during his school years have always been bilaterally normal. His early speech and language development were thought to be normal. He finished school without any additional educational support and obtained three O and one A levels. He is now working in his parents' flower shop.

He was first seen for a central auditory assessment six and one-half years after diagnosis at the age of 32 years. At present, he reports severe difficulties understanding speech in background noise, conducting a telephone conversation, or listening to the radio. He uses subtitles when watching television. He does not appreciate and does not listen to any kind of music and sings out of tune. He believes that these hearing difficulties have been present since his childhood and have not changed over the years.

## METHODS

### Baseline Audiometric Investigations

#### *Pure-Tone Audiometry*

Pure-tone audiometry was carried out using a GSI 61 audiometer with TDH-49 earphones in a sound proof room, following

the procedure recommended by the British Society of Audiology (BSA, 1981).

#### *Tympanometry and Acoustic Reflexes*

Tympanometry was obtained with a probe signal continuous 226 Hz tone at 85 dB SPL using a GSI-33 Middle Ear Analyser. 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 ipsilateral and contralateral 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 abnormal if they exceeded 105 dB HL at two or more adjacent frequencies or if the interaural threshold difference exceeded 10 dB on at least two adjacent frequencies (Cohen and Prasher 1988).

#### *Otoacoustic Emissions*

The presence of otoacoustic emissions indicates that the preneural cochlear receptor as well as the middle ear mechanism gives a normal response to sound. Otoacoustic emissions tests were carried out in both ears using the ILO88/92 Otodynamic Analyser, with a standard default setup (Kemp et al, 1990).

#### *Auditory Brainstem Evoked Responses (ABR)*

ABR were recorded with the Spirit 2000 Nicolet equipment. Electrodes were placed at the vertex (Cz) and on each mastoid (A1 and A2), the nontest mastoid being used as ground. Monaural 100  $\mu$ s click stimuli alternating in polarity were presented at a rate of 11.1 per second and at 90 dB nHL via TDH-49 headphones. Electrode impedance was less than 5 kohm. The electrical activity was amplified and filtered (150–3000 Hz, 12 dB per octave roll-off). A total of 1024 responses were given for each average, with an averaging window of 10 msec and an artifact-rejection feature set at 25  $\mu$ V peak to peak. 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 (1994).

**Central Auditory Tests**

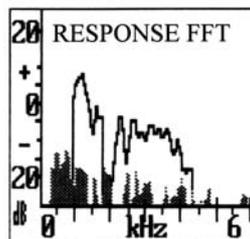
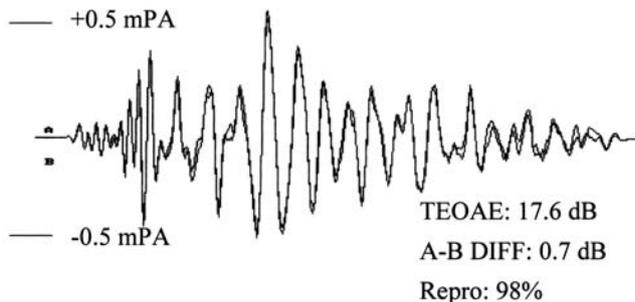
We used a test battery that consisted of two standard tests, the dichotic digits and frequency pattern tests, and one experimental temporal gap detection procedure, the gaps-in-noise (GIN) test. We also conducted auditory event-related potentials (AEPs) to complex harmonic tones.

The dichotic digits test (Musiek, 1983) is composed of naturally spoken single digits from 1 to 9, excluding 7. The two ears are simultaneously presented with a different pair of digits at 50 dB SL, and the listener has to repeat all four digits. After a brief practice session, the listener was administered a list of 40 paired digits in each ear.

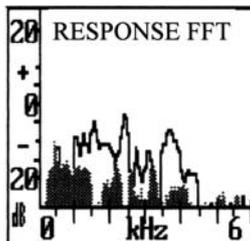
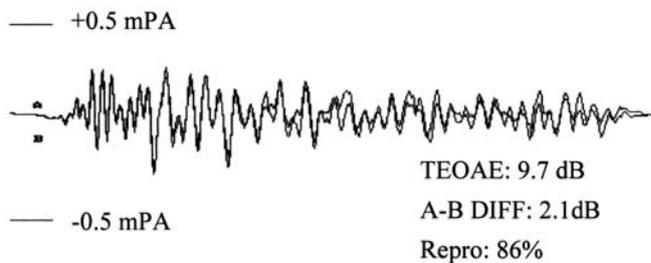
In the frequency pattern test (Musiek 1994), the test stimuli consist of three tone-burst sequences, which are a combination of a low-frequency (880 Hz) and a high-frequency (1122) tone. Each sequence is composed of two bursts of the same and one burst of a different frequency. A total of 30 patterns were presented to each ear at 50 dB SL after a brief practice session. The listener is required to name the sequence (e.g., high-high-low).

In the gaps-in-noise test (Musiek, n.d.), the patient is monaurally presented with a 6 sec burst of white noise in which 0–3 gaps of varying duration (2 msec to 20 msec) are embedded. The patient has to identify the number of gaps in each noise burst. This test provides two scores, the correct detection

**CLICK TEOAES**

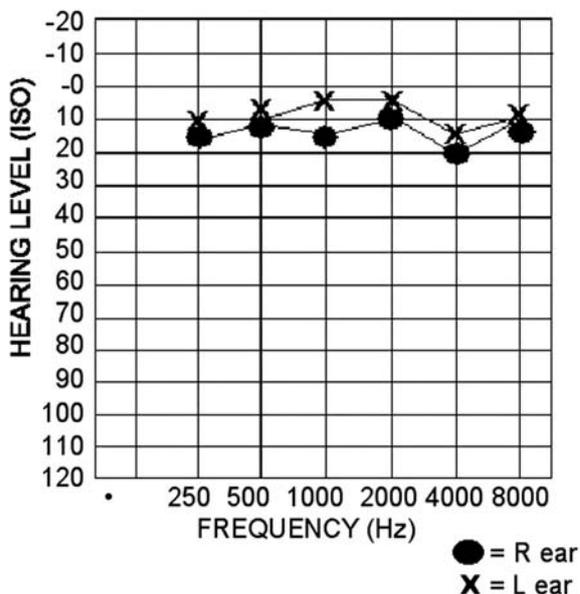


Right ear



Left ear

**Figure 2.** The patient's transient otoacoustic emissions (normal in both ears).



**Figure 1.** The patient's audiogram was normal in both ears.

score (percent of correct answers) and the gap detection threshold, which is defined as the shortest gap duration that the patient can correctly identify in 50% of the trials (i.e., in three out of six trials for each gap duration).

**RESULTS**

**Baseline Audiometric Tests**

C had normal audiometric thresholds (Figure 1), tympanograms, and otoacoustic emissions

Table 1. ABR Results

Latency (msec)	I	III	V	I-III	I-V	III-V
R ear	1.48	3.9	6.2	2.41	4.72	2.3
L ear	1.46	4.06	6.28	2.60	4.82	2.22

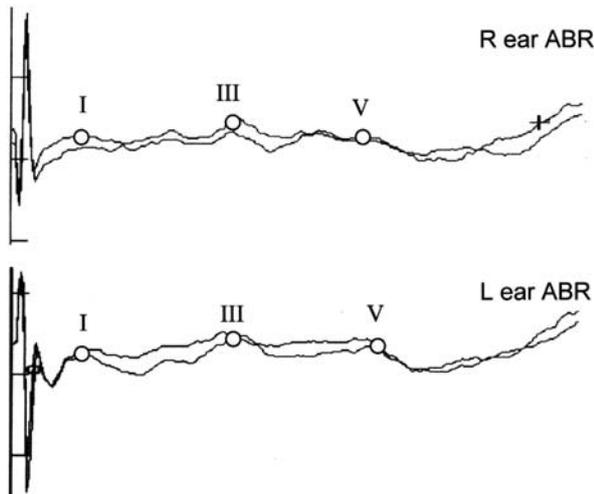


Figure 3. ABR results. Positivity plotted upward. See Table 1 for information.

(Figure 2). His acoustic reflexes were absent both ipsilaterally and contralaterally at 2 and 4 kHz, indicating a low brainstem lesion (Cohen and Prasher, 1988). In reference to our clinical norms, his auditory brainstem evoked responses waves I and III were bilaterally present at normal latencies, but waves V were bilaterally delayed (right: 6.2 msec and left: 6.28 msec) and of poor morphology. Interwave intervals I-III, I-V, and III-V were bilaterally delayed (Table 1 and Figure 3).

### Central Auditory Tests

Dichotic digits test: C achieved a score of 85% in the right and 27.5% in the left ear (Normal scores: 90% or better for each ear).

Frequency pattern test: C achieved 30% in the left and 50% in the right ear (Normal: better than 80%).

Gaps-in-noise test: He obtained a detection threshold of 12 msec in both ears

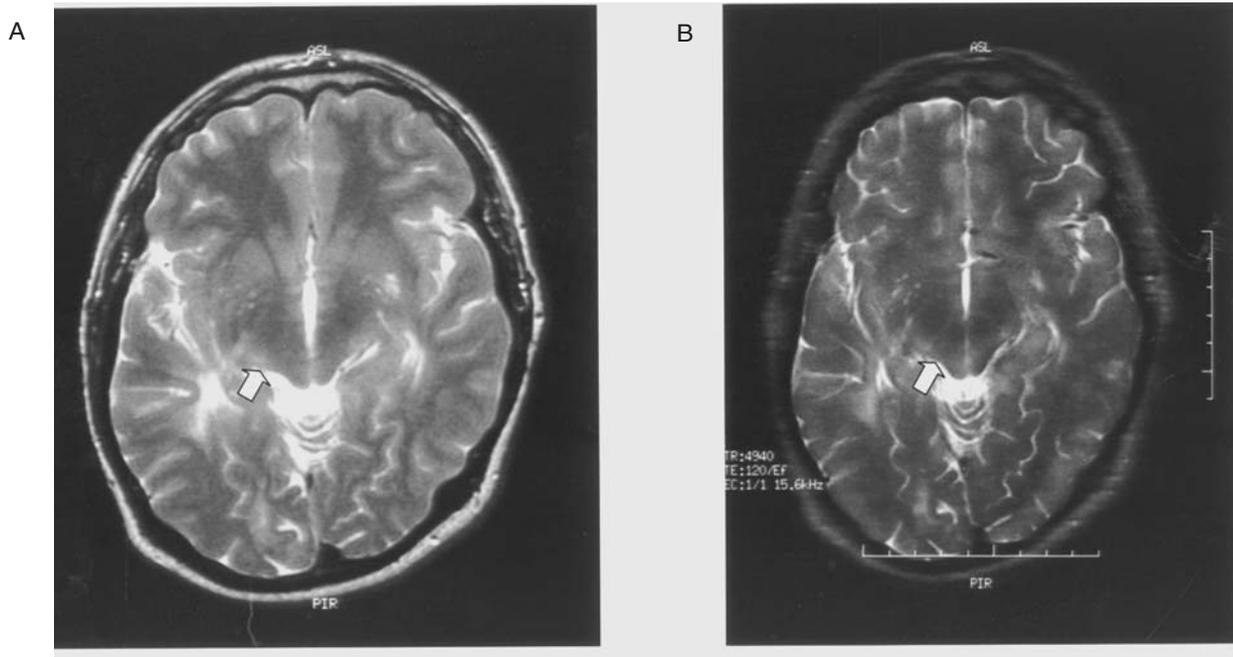
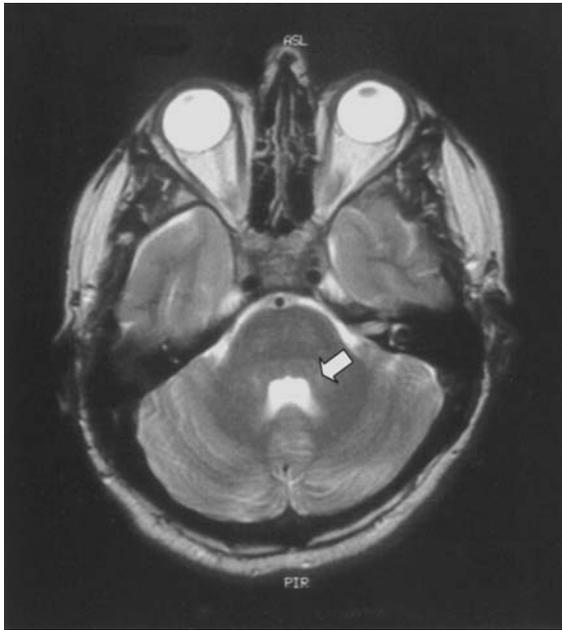


Figure 4. Two images from spin echo acquisitions with mainly T2 dependent contrast through the upper mid-brain at about 45° from its true transverse plane (A) is 5 mm and (B) is 3 mm in thickness. Because of the angle of the section plane, the colliculi shown in both are the superior, and signal change is visible extending medially from the posterior sublentiform part of the internal capsule into the low and almost flat elevation of the medial geniculate body (arrow) and at least the lateral part of each inferior brachium (clearer on the left side due to slight lateral tilt of the slice).

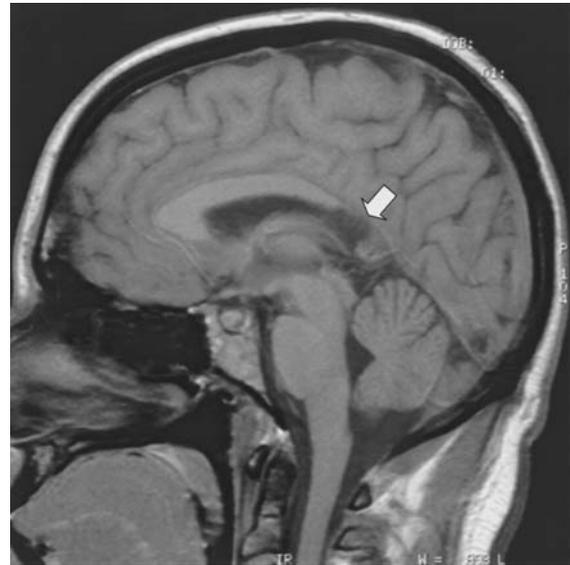


**Figure 5.** MRI section in the same plane as Figure 4, with similar T2 dependent contrast through the middle of the pons, 5 mm in thickness. The transverse striations of the scattered corticospinal fibers bundles at the level of the basis pontis are just visible here, and a similarly subtle change in the region of each trapezoid body and more laterally the supra olivary nuclear complexes just anterior to the lower extremity of each parabrachial sulcus in this oblique section (arrow).

with correct detection scores 30% on the right and 36% on the left ear. His gap detection threshold exceeded the mean of five age-matched, male, right-handed normal controls (mean detection threshold 4.6 msec, SD = 0.74) by more than 3 standard deviations, while his correct detection score was well below 3 SD from the mean of these controls (mean correct detection score of 68%, SD = 8).

### MRI BRAIN

A series of MRI studies from 1995 to 2003 showed a similar pattern and extent of largely symmetrical confluent signal change in the deep white matter of the posterior part of both cerebral hemispheres, especially adjacent to the trigone region of each lateral ventricle. There was evidence of greater loss of white matter bulk on the left side. Clear involvement of the retro and posterior sublenticular parts of the internal capsules was evident, which faded into imperceptibility in the white matter of the posterior part of



**Figure 6.** Midline sagittal MRI section 5mm thick with T1 dependent contrast. It shows extreme thinning of the posterior part of the corpus callosum (arrow).

the transverse temporal gyri. More medially clear involvement of each inferior brachium was visible. Pontine signal changes were subtle but included a transverse banded appearance in the upper part basis pontis, converging in its lower part into the corticospinal part, perhaps indicating secondary degeneration. However, similar subtle changes were present in the ventral part of the pontine tegmentum in the expected location of the trapezoid bodies and medial lemnisci. Finally, there was marked signal change and volume loss in the posterior part of the sulcus of the corpus callosum and anterior splenium (see Figures 4 to 6).

### DISCUSSION

Auditory processing difficulties were the presenting and sole manifestation of the cerebral form of X-linked adrenoleukodystrophy in our patient. Despite the fact that these symptoms had been present since childhood, they were dismissed due to the finding of repeatedly normal audiograms. It is thus noteworthy that the diagnosis of X-ALD in our patient would have been missed, were it not for his thorough investigation following the diagnosis of X-ALD in his brother, who had a rapidly progressive neurological

deterioration with an early death. This highlights the need for thorough audiological evaluation of the patient who complains of hearing difficulties in the presence of a normal audiogram. It also raises the question of whether auditory processing deficits may exist in the forms of ALD that are otherwise labelled as “asymptomatic.”

Hearing difficulties in the presence of a normal audiogram are among the most frequently reported initial symptoms in the childhood cerebral form of X-ALD (Moser et al, 2001), and these symptoms may progress to complete verbal agnosia in some cases (Oka et al, 1996). However, with the exception of the literature reporting on electrophysiology findings, there are few papers describing the nature and course of the auditory deficits in X-ALD. Central auditory tests indicated the presence of several auditory processing deficits in our patient. These included:

- a. Delayed central conduction time as indicated by the delayed ABR.
- b. Poor temporal acuity, as indicated by the gaps-in-noise test.
- c. Poor ability to sequence sounds and identify patterns, as indicated by the frequency pattern test.
- d. A severe left ear deficit in the dichotic situation.

The central auditory test findings correlated well with the patient-reported hearing difficulties, which included severe difficulties with understanding speech in noisy environment, distorted or degraded speech, and a lack of appreciation of music. Thus, his lack of appreciation of music would be consistent with his severe sequencing and other temporal processing difficulties, and poor results in a gaps-in-noise test have been reported to correlate with poor speech understanding in competing fluctuating background (Snell et al, 2002).

The patient's behavioral and electrophysiological test results could be explained by the distribution of pathology in his brain MRI, which showed the characteristic pattern of abnormalities that is observed in up to 80% of X-ALD patients (Loes et al, 1994). Thus, the findings of delayed ABR interwave intervals I-III, I-V, and wave V, and the absent acoustic reflexes would be consistent with mild changes in the low brainstem. Prolonged central conduction time in auditory brainstem evoked

responses is a common and well-reported finding in X-ALD (e.g., Shimizu et al, 1988), with a progressive deterioration in the ABR that parallels the progress of demyelination in the brainstem (Kaga et al, 1980). Despite the lack of one-to-one correlation between the ABR waveforms and distinct anatomical structures (Jacobson 1994), peak I broadly corresponds to the distal portion of the VIIIth nerve, peak III to the cochlear nucleus, and wave V to the termination of lateral lemniscus axons at the inferior colliculus (Möller 1994). Acoustic reflex thresholds may provide additional information regarding the low brainstem and are reported to have a 70% sensitivity in identifying intrinsic brainstem lesions (Cohen and Prasher 1988). For the ipsilateral reflex, the seventh nerve nucleus receives input from the ventral cochlear nucleus (VCN) predominantly via the trapezoid body and to a lesser extent via the ipsilateral superior olivary complex (SOC). For the contralateral reflex, the seventh nerve nucleus receives afferents from the contralateral VCN via the contralateral SOC (Webster, 1992). The abnormal ABR and ARTs in our patient could thus correspond to the finding of a striatal appearance in the area of the trapezoid body on the brain MRI.

The marked left ear deficit in the dichotic digits test and the abnormal scores in the frequency pattern test could similarly be well explained by the MRI findings and by the severe reduction in size of the posterior corpus callosum in particular, as both tests require hemispheric transfer of the auditory information. In dichotic speech tests, the contralateral pathway dominates; thus, input from the left cochlea will go to the right hemisphere and will have to cross to the left (language) hemisphere via the corpus callosum, for a verbal report to be made possible (Musiek and Pinheiro, 1985). In the frequency pattern test, the right hemisphere determines the pattern of the sequence as a gestalt, but the labeling of the sequence happens at the left (language) hemisphere, and the task requires that information from the right hemisphere is transferred to the left via the corpus callosum (Pinheiro and Musiek, 1985). However, the results in these two tests could also to some extent be due to the bilateral involvement of the medial geniculate body, lateral lemnisci, and internal capsules (Musiek et al, 1994).

Another interesting aspect of this case was the lack of deterioration, which was documented for seven years since the diagnosis but which may have lasted for more than 25 years, since early childhood, when the patient initially complained of the hearing difficulties. The finding of an abnormal brain MRI in X-ALD has serious prognostic implications, but there are exceptions (Moser et al, 2000). In some rare cases of cerebral ALD, arrest or extremely slow deterioration of the clinical picture and the underlying demyelination has been reported for periods of up to 12 years (Korenke et al, 1996) or longer (Cavaletti et al, 1990), and it is not clear what factors are responsible for this milder phenotype.

In conclusion, this is a rare case of X-linked adrenoleukodystrophy with severe central auditory processing deficits in the presence of demyelinating lesions of auditory and other parts of the brain. The patient has been free of other neurological symptoms or adrenal dysfunction, and no deterioration has been noted over a period of at least seven and possibly up to 25 years. The patient has been given auditory training, in order to encourage the brain's plasticity and to help ameliorate his hearing deficits, and he will continue to be monitored. This case highlights the importance of fully investigating the patient-reported hearing complaints in the presence of a normal audiogram. It also suggests that audiological investigations may be of value in the phenotypic evaluation of adrenoleukodystrophy.

## REFERENCES

- British Society of Audiology. (1981). Recommended procedure for pure tone audiometry using a manually operated instrument. *Br J Audiol* 15:213–216.
- Cavaletti G, Boglium G, Tredici G. (1990). Adrenoleukodystrophy. Report of a case with extremely slow progression of symptoms. *Acta Neurol* 12:109–114.
- Cohen M, Prasher D. (1988). ABR and ART in neurological diagnosis. *Scand Audiol* 17:153–162.
- Jacobson GP, Jacobson JT, Ramadan N, Hyde M. (1994). 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.
- Kaga K, Tokoro Y, Tanaka Y, Ushizima H. (1980). The progress of adrenoleukodystrophy as revealed by auditory brainstem evoked responses and brainstem histology. *Arch Otol Rhinol Laryngol* 228:17–27.
- Kemp DT, Ryan S, Bray P. (1990). A guide to the effective use of Otoacoustic Emissions. *Ear Hear* 11:93–105.
- Korenke GC, Pouwels PJ, Frahm J, Hunneman DH, Stoeckler S, Krasemann E, Jost W, Hanefeld F. (1996). Arrested cerebral adrenoleukodystrophy: a clinical and proton magnetic resonance spectroscopy study in three patients. *Pediatr Neurol* 15:103–107.
- Loes DJ, Hite S, Moser H, Stillman AE, Shapiro E, Lockman L, Latchaw RE, Krivit W. (1994). Adrenoleukodystrophy: a scoring method for brain MR observations. *Am J Neuroradiol* 15:1761–1766.
- Migeon BR, Moser HW, Moser AB, Axelman J, Sillence D, Norum RA. (1981). Adrenoleukodystrophy: evidence for X linkage, inactivation, and selection favoring the mutant allele in heterozygous cells. *Proc Natl Acad Sci USA* 78:5066–5070.
- Möller AR. (1994). Neural generators of auditory evoked potentials. *Semin Hear* 19:11–27.
- Moser HW, Loes DJ, Melhem ER, Raymond GV, Bezman L, Cox CS, Lu S. (2000). X-linked Adrenoleukodystrophy: overview and prognosis as a function of age and brain magnetic resonance imaging abnormality. A study involving 372 patients. *Neuropediatrics* 31:227–239.
- Moser HW, Smith KD, Watkins PA, Powers J, Moser AB. (2001). X-linked Adrenoleukodystrophy. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*. 8th edition. New York: McGraw Hill.
- Mosser J, Lutz Y, Stoeckel ME, Sarde CO, Kretz C, Douar AM, Lopez J, Aubourg P, Mandel JL. (1994). The gene responsible for adrenoleukodystrophy encodes a peroxisomal membrane protein. *Hum Mol Genet* 3:265–271.
- Musiek FE. (1983). Assessment of central auditory dysfunction: the Dichotic Digit Test revisited. *Ear Hear* 4:79–83.

Musiek FE. (1994). Frequency (pitch) and duration pattern tests. *J Am Acad Audiol* 5:265–268.

Musiek FM, Baran JA, Pinheiro ML. (1994). *NeuroAudiology: Case Studies*. San Diego: Singular Publishing Group.

Musiek FE, Pinheiro ML. (1985). Dichotic speech tests in the detection of central auditory dysfunction. In: Musiek FE, Pinheiro ML. *Assessment of Central Auditory Dysfunction: Foundations and Clinical Correlates*. Baltimore: Wakerly Press.

Oka A, Saito M, Kubota M, Sakakihara Y, Yanagisawa M. (1996). Temporary improvement of neurological symptoms with gammaglobulin therapy in a boy with adrenoleukodystrophy. *Brain Dev* 18:119–121.

Pinheiro ML, Musiek FE. (1985). Sequencing and temporal ordering in the auditory system. In: Musiek FE, Pinheiro ML. *Assessment of Central Auditory Dysfunction: Foundations and Clinical Correlates*. Baltimore: Wakerly Press.

Schwartz DM, Morris MD, Jacobson JT. (1994). The normal Auditory Brainstem Response and its variants. In: Jacobson JT, ed. *Principles and Applications in Auditory Evoked Potentials*. London: Allyn and Bacon.

Shimizu H, Moser HD, Naidu S. (1988). Auditory brainstem response and audiologic findings in adrenoleukodystrophy: its variant and carrier. *Otolaryngol Head Neck Surg* 98:215–220.

Snell KB, Mapes FM, Hickman ED, Frisina DR. (2002). Word recognition in competing babble and the effects of age, temporal processing, and absolute sensitivity. *J Acoust Soc Am* 112:720–727.

Webster DB. (1992). An overview of mammalian auditory pathways with an emphasis on humans. In: Webster DB, Popper AN, Fay RR, eds. *The Mammalian Auditory Pathway: Neuroanatomy*. London: Springer-Verlag.