

# Early-Onset Sensorineural Hearing Loss in a Child with Turner Syndrome

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## Abstract

Turner syndrome is among the more common but less familiar syndromes that include sensorineural hearing loss and middle ear disease. This article provides a review of the syndrome, an illustrative case, and a review of specific issues relevant to audiologic management of patients with Turner syndrome.

**Key Words:** Conductive hearing loss, sensorineural hearing loss, Turner syndrome

**Abbreviations:** GH = growth hormone, TS = Turner syndrome

**T**urner syndrome (TS) is one of the most common human chromosome anomalies, occurring in approximately 1:2000 female live births (Nielsen and Wohlert, 1991). Girls with TS have an abnormal or missing X chromosome that commonly causes short stature, lymphedema, cardiac abnormalities, gonadal dysgenesis, dysmorphic features, and a variety of other problems including hearing loss and recurrent middle ear disease (Lippe, 1996; Saenger, 1996). The phenotypic expression of TS is very broad with part of the variability due to differences in karyotype (Fig. 1) (Ogata and Matsuo, 1995). Generally, girls with a 45,X karyotype (missing an entire X chromosome) are more severely affected than those with a structural abnormality of the X chromosome or mosaicism (i.e., having more than one cell line; e.g., 45,X/46,XX)

## HEARING LOSS AND TURNER SYNDROME

**A**n association of TS with hearing loss and otitis media was recognized in the late 1960s (Szpunar et al, 1968). In 1969, Anderson

et al in Sweden presented audiometric and otologic data from 79 patients. Nearly 70 percent of the infant and young adult patients they studied had a history of middle ear infections and 64 percent had documented sensorineural or mixed hearing loss. A characteristic mid-frequency dip was noted for patients with sensorineural loss.

Watkin (1989) studied retrospective hearing data on younger patients with TS recruited from hospitals and schools in the United Kingdom. The mean age was 10 years, 4 months, with an age range of 18 months to 27 years, 9 months. Ten of the 24 subjects had sensorineural or mixed hearing loss. The mean age of the subjects with pure sensorineural loss was 17.8 years, considerably higher than the mean age of those with purely conductive (4.5 years) or mixed hearing losses (12 years). For three subjects, there was evidence of progressive sensorineural hearing loss, with onset apparently after the age of 7 years.

A study of 22 patients with TS recruited from the Endocrinology Department at Children's Hospital of Pittsburgh (Sculerati et al, 1990) demonstrated that hearing loss may have an even earlier onset. Although patients were mostly teenagers, the age range was 3 to 38 years. Only 27 percent of these patients had normal hearing, whereas 36 percent had purely conductive hearing losses and 37 percent had sensorineural or mixed hearing losses. The conductive losses were associated with otitis media or ossicular degeneration following chronic middle ear disease. Computed tomographic (CT) scans of temporal bones in six patients revealed

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**Figure 1** As illustrated in these photographs, the phenotypic expression of Turner syndrome is very broad, due in part to differences in karyotype. *Left*, Nine year old diagnosed at birth; 45X karyotype; severe web neck, prominent ears, and mild ptosis. *Middle*, Two year old diagnosed at birth; 45X karyotype; epicanthal folds and posteriorly rotated ears. *Right*, Fourteen year old diagnosed at 12 years of age for short stature; 46,X,i(Xq).

a downward slant of the external auditory canals but no anomalies of the otic capsule.

Hultcrantz et al (1994) in Sweden have reported several investigations of hearing loss in patients with TS. In a study of 44 middle-aged women, Hultcrantz et al (1994) reported "significant hearing problems" for 60 percent of their subjects, and 27 percent were reported to be using hearing aids. The audiograms for patients with sensorineural hearing loss were characterized by a mid-frequency dip in the 1000- to 2000-Hz range. Interestingly, women with the karyotypes 45,X and 45,X/46,X,i(Xq) showed the highest incidence of sensorineural hearing loss. A subsequent study by Hultcrantz and Sylven (1997) examined hearing disorders in women aged 16 to 34 years with TS. The usual high incidence of middle ear infections was demonstrated and, as in the previous study, a mid-frequency sensorineural hearing loss was present in over three-quarters of their 40 subjects. In addition, these investigators reported preliminary data indicating that the mid-frequency dip first appeared between the ages of 5 and 9 years of age. These findings are consistent with those of Stenberg et al (1998), who noted a mid-frequency dip in 58 percent of the 56 girls they studied, ranging in age from 4 to 15 years. The youngest subject with mid-frequency loss was 6 years old. These authors also reported that the average mid-frequency loss in their sample had a mean of 18.8 dB HL, a degree of hearing loss that would not have been detected in a routine 20 dB HL pure-tone

hearing screening. Based on these findings, Stenberg et al emphasize the importance of obtaining air- and bone-conduction thresholds for any child suspected of having TS.

Recently, a group of Turkish investigators reported prospective audiologic and otologic data for 38 phenotypic females with TS (Gungor et al, 1999). In addition to conventional audiometry, they obtained thresholds for a series of ultra-high audiometric frequencies (8–18 kHz). Their findings revealed histories of recurrent middle ear disease in approximately 68 percent of the patients and evidence of a sensorineural or mixed loss in 21 percent of the subjects, based on conventional audiometric assessment. Interestingly, examination of the ultra-high audiometric frequencies revealed that nearly every patient (98.7%) exhibited elevated pure-tone thresholds, independent of age and karyotype.

Hultcrantz and Sylvén (1997) note that differences between studies with regard to the number of subjects exhibiting the characteristic sensorineural hearing loss may be explained by different ages of the subjects and the manners in which the loss is calculated. For example, some investigators included children who were so young that the dip may not yet have developed. Others may not have considered mid-frequency dips to be pathologic if they did not exceed the 20 dB HL criteria of hearing within normal limits. Finally, the overlay of additional high-frequency hearing loss (early presbycusis) in older subjects may have a masking effect on the characteristic mid-frequency dip.

### **ETIOLOGY OF CONDUCTIVE HEARING LOSS**

The underlying cause of the conductive hearing loss frequently observed in girls with TS is clearly related to the high prevalence of middle ear disease in this population. As noted previously, the high prevalence of otitis media seems to result from the abnormally horizontal orientation of the eustachian tube, which results in poor drainage and inadequate ventilation of the middle ear space. Furthermore, the shorter length of the eustachian tube may allow more nasopharyngeal microorganisms to reach the middle ear.

### **ETIOLOGY OF SENSORINEURAL HEARING LOSS: GROWTH FACTORS, HORMONAL, AND OTHER METABOLIC INFLUENCES**

The etiology of the sensorineural hearing loss frequently noted in girls with TS is less clear than the etiology of the conductive component. A few investigators have studied the potential role of insulin-like growth factor-I (IGF-I) and various hormones in the development of the auditory system (Verp et al, 1988; Ayer-Le-Lievre, 1991; Bondy, 1991; Represa et al, 1991; Varela-Nieto et al, 1991; Leon et al, 1995; Barreca et al, 1997). For example, IGF-I, a growth-hormone (GH)-dependent protein, stimulates growth in the cochleovestibular ganglion and is present in the cochlear epithelium (Leon et al, 1995; Ayer-Le-Lievre, 1991), as well as in the synaptic stations of the auditory system including the cochlear nucleus, superior olive, lateral lemniscus, medial geniculate body, and inferior colliculus (Bondy, 1991). IGF-I may regulate proliferative growth of the otic primordium during normal development (Leon et al, 1995) and play a role in the shaping of synaptic connections or myelination (Bondy, 1991). Consequently, it is hypothesized that reduction of IGF-I or desensitization of its signaling pathways could detrimentally affect the growth and development of the auditory system leading to sensorineural hearing loss. Although GH is used in pharmacologic doses to enhance growth of girls with TS, there is no consistent evidence for GH or IGF-I deficiency in these girls.

The vast majority of girls with TS have ovarian dysfunction. Auditory brainstem and middle latency evoked potentials in laboratory animals suggest relationships between ovar-

ian hormones and both central auditory and cochlear function (Coleman et al, 1994). Relationships between progesterone therapy and cochlear blood flow (Laugel et al, 1988), as well as relationships between thyroid hormones and hearing (Haubrich, 1975), have also been demonstrated in animals.

### **ETIOLOGY OF SENSORINEURAL HEARING LOSS: GENETIC FACTORS**

Sculerati et al (1997) and others have stated that the lack of radiographic evidence of otic capsule malformations in girls with TS suggests that the lesion causing sensorineural hearing loss in TS most likely involves the membranous cochlea. However, the cause of the suspected damage remains unknown. Based on cytogenetic and molecular genetic studies, Sculerati et al suggested the possibility that variable expression of a paternal recessive X-linked gene for hearing loss may be responsible for sensorineural hearing loss in Turner girls. Hultcrantz et al (1994) suggested that a genetic defect leading to "premature aging of the cochlea" may explain why sensorineural hearing loss has been found at a younger age in women with TS, particularly those with 45,X and 45,X/46, X,i(Xq) karyotypes, compared to age-matched controls. Hultcrantz and Li (1993) cite evidence from animal studies suggesting that genetically damaged hair cells appear to be more susceptible to noise and other potentially damaging stimuli throughout life.

As noted by Hultcrantz and Sylvén (1997), this premature aging of the cochlea characterized by an early high-frequency hearing loss (which appears in addition to the mid-frequency dip) is also seen in Down syndrome, another chromosomal disorder. In Down syndrome, a form of early presbycusis (high-frequency hearing loss) is seen beginning around the second to third decade. Buchanan (1990) suggested that the findings in patients with Down syndrome might be due to a shorter cochlea and/or defects in the cochlear ganglion. Although otic capsule defects have not been found in Turner patients, the possibility of cochlear ganglion defects has not been ruled out.

### **AUDITORY PROCESSING IN TURNER SYNDROME**

There is evidence that some children with TS have difficulty processing auditory information even if hearing sensitivity is within normal

limits (Holmes et al, 1984; Walzer and Stanley, 1985; Williams et al, 1991). Specifically, deficits in auditory rate processing, immediate auditory recall, and/or expressive language have been reported in children with X-chromosome abnormalities (Walzer and Stanley, 1985). As noted above, auditory brainstem and middle latency evoked potentials in laboratory animals suggest relationships between ovarian hormones and both central auditory and cochlear function (Coleman et al, 1994). Further studies are needed in girls with TS that include physiologic and behavioral assessment of central auditory processing.

### CASE PRESENTATION

**K**C is an 18-year-old white female who was diagnosed with TS at the age of 12.8 years during an evaluation for short stature and pubertal delay. Medical history revealed an uncomplicated pregnancy and delivery with a birth weight of 2707 gm. There was no history of lymphedema. Review of KC's growth chart revealed that growth had been poor since birth, with her height falling below the 5th percentile by 2 years of age. Her medical history was otherwise unremarkable except for the presence of sensorineural hearing loss. She had no history of recurrent otitis media.

KC was managed audiologically through a private ENT office from the age of 5 years. The assessment occurred at the request of her parents, who reported that she seemed to have diminished hearing for as long as they could remember. Behavioral pure-tone audiometry revealed a mild bilateral mid-frequency sensorineural hearing loss (Fig. 2A); speech recognition was excellent. Follow-up evaluation at 7 years of age revealed further progression of hearing loss in the mid-frequency range, although speech recognition remained excellent, bilaterally, for monosyllabic words presented at a comfortable level above threshold (Fig. 2B). She was seen again at 9 years of age and the audiogram showed further progression of the sensory component (Fig. 2C). KC was reported to hear well in a quiet listening situation, but conversation was difficult in noisy environments such as the school cafeteria. There was a history of hearing loss in the mother and the maternal grandmother, neither of whom used hearing aids. There was no family history of pubertal delay or extreme short stature. KC was an excellent student but reported that math was difficult for her.

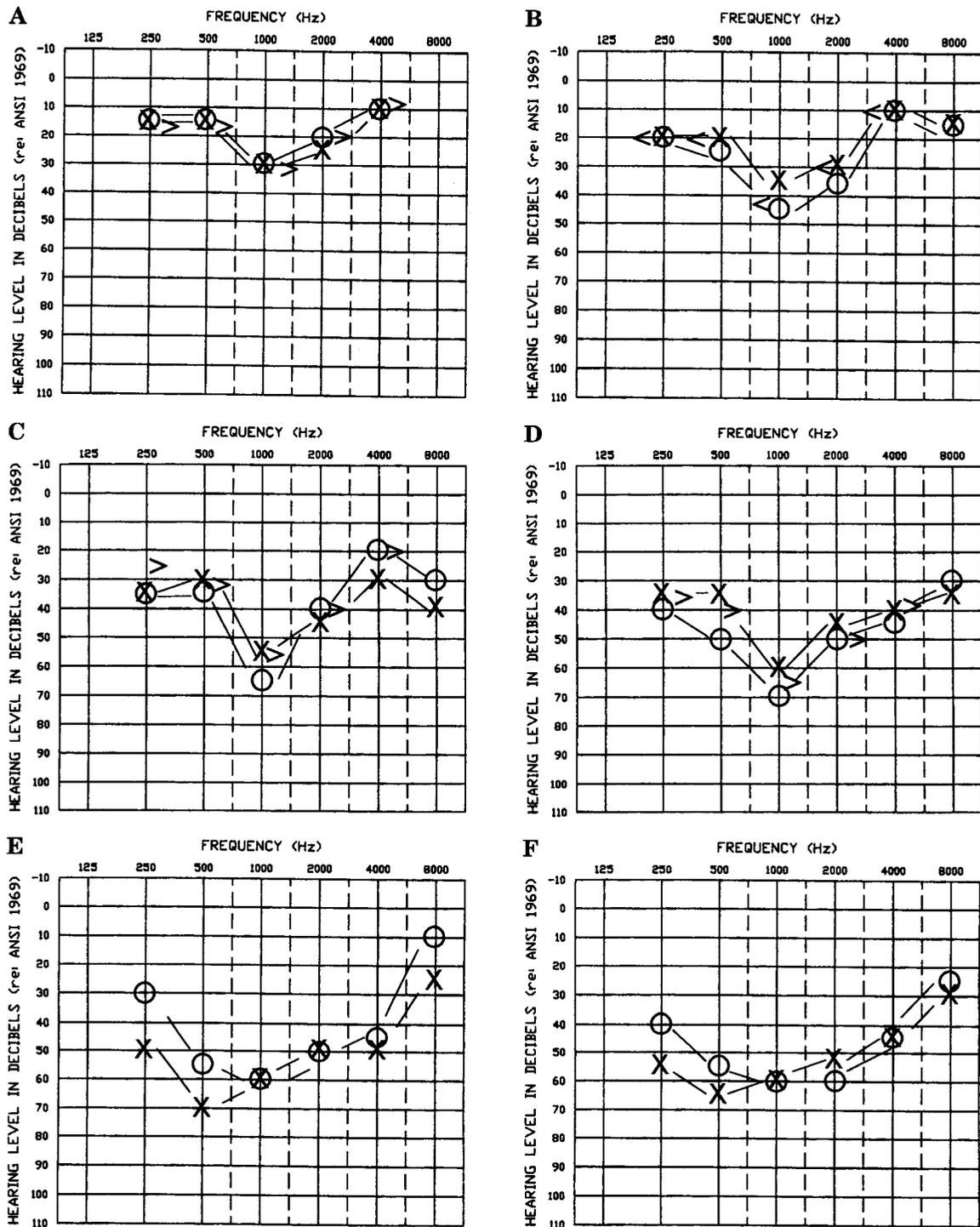
At the age of 12.8 years, KC was referred by her pediatrician to a pediatric endocrinologist for evaluation of short stature. At the time of her initial endocrine evaluation, her height was 124.3 cm, below the 3rd percentile and equivalent to the average height of a 7.5 year old girl. Her physical examination was remarkable for several physical stigmata of TS including a low posterior hairline, epicanthal folds, retrognathia, nails that were hypoplastic and deeply inset, cubitus valgus, and multiple nevi. She did not have a high arched palate or webbed neck. Tympanic membranes were described as normal. Cardiac, pulmonary, and abdominal examinations were unremarkable. She had no breast development; genitalia were normal for a prepubertal girl.

A karyotype confirmed the diagnosis of TS, revealing a mosaic pattern in which some cells were 45X and others contained 46 chromosomes with a structurally abnormal Y. Screening echocardiography and renal ultrasound evaluations were normal. Because of the increased risk of tumors developing in gonads that contain Y chromosome material, she underwent laparoscopic removal of her ovaries. GH therapy was begun.

At the age of 13, the audiogram showed further progression of sensorineural hearing loss (Fig. 2D). There was no evidence of middle ear disease. Word recognition scores remained excellent (95% and 92% for right and left ears, respectively); however, speech reception thresholds (SRTs) had decreased to 40 to 50 dB. KC complained of significant communication problems related to her hearing loss and arrangements were made for preferential seating in the classroom. Hearing aid use was discussed with the family, and 4 months later, at the age of 14 years, trial use of binaural amplification was initiated. Hearing aid use was judged to be beneficial, and KC has used binaural in-the-ear instruments ever since. Subsequent audiograms (Figs. 2E and 2F) show further progression.

This patient is now 18 years old. Her current height measures 146.6 cm, approximately 9 cm taller than that expected without GH therapy. Estrogen therapy was delayed until 15 years of age to allow for additional growth. She now receives cyclic estrogen and progesterone therapy and has regular menses on this regimen.

Hearing loss has been a growing problem for several years and remains a significant concern, even though she is now using binaural amplification. Her parents report that KC frequently demonstrates hearing difficulty but is



**Figure 2** Pure-tone audiograms for KC at age 5 (A); age 7 (B); age 10 (C); age 13 (D); age 16 (E); and age 18 (F). O = right ear, air-conduction threshold; X = left ear, air conduction threshold; < > = bone conduction threshold recorded from the right or left mastoid, respectively. Bone-conduction thresholds were unavailable for audiograms E and F but are presumed to be pure sensorineural since there is no history of middle ear disease or conductive impairment.

reluctant to request clarification or to converse in general. Her hearing problems have reportedly contributed to difficulties with socialization and intermittent episodes of depression.

#### COMMENT

This case has several important clinical implications for audiologists. First, it demon-

strates that sensorineural hearing loss associated with TS can occur in the preschool years or earlier. Second, it clearly illustrates the progression that often characterizes sensorineural hearing loss in this population and the need for careful audiologic monitoring and management. Third, it demonstrates the importance of genetic counseling for children with sensorineural hearing loss of unknown etiology.

KC's hearing loss was first documented at age 5; this was approximately 7 years before the diagnosis of TS. We were unable to determine the age of onset for KC's hearing loss, but, based on parental report, a mild hearing loss may have been present from birth. Although the age of onset and natural history of hearing loss in TS have not been thoroughly investigated, this case shows that the sensorineural hearing loss in TS, with its characteristic audiometric configuration, can begin early in life and progress during childhood and adolescence.

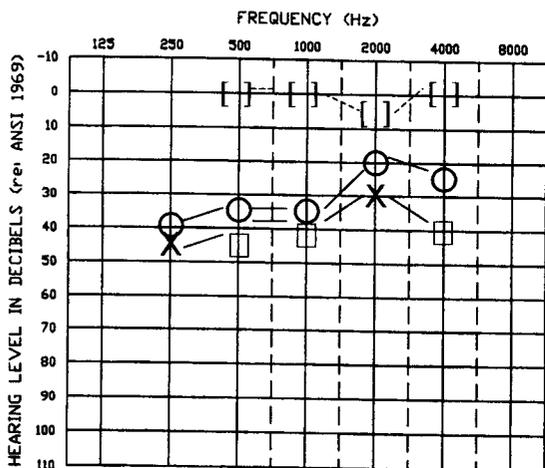
The case is also important because it illustrates the potentially key role of the audiologist in the initial identification of TS. Lymphedema leading to the diagnosis of TS during infancy occurs in only 20 to 40 percent of girls; short stature leads to the diagnosis of most others in childhood or adolescence. Thus, the diagnosis of TS may be delayed for several years after the child has fallen below the 5th percentile for height, as in this case, where the child had been short since 2 years of age. Although not all patients with TS experience hearing loss, it is among the more common genetic syndromes known to include hearing loss. Consequently, the audiologist may be the first professional to suspect TS. Referral to a pediatric endocrinologist should be considered in any child with mid-frequency sensorineural hearing loss or in a child with chronic otitis media who has unexplained short stature and/or a history of lymphedema or pubertal delay. Early diagnosis is important for maximizing the growth and development of girls with TS. Early GH therapy accelerates growth and may allow for earlier initiation of therapies for pubertal development, improved social interactions (Huisman et al, 1993; Rovet et al, 1993), and improved final adult stature (Donaldson, 1997; Rosenfeld et al, 1998; Sas et al, 1999). Early diagnosis also allows for timely screening and intervention for other problems, including strabismus, renal abnormalities, learning disabilities, and hearing loss.

Because the sensorineural hearing loss associated with TS is often characterized by normal or near-normal sensitivity in the low and high frequencies, it is possible that the loss will be

missed by routine hearing screening procedures such as automated auditory brainstem response testing or pure tone screening. Thus, diagnostic frequency-specific physiologic and/or behavioral audiologic assessment procedures should be provided whenever a diagnosis of TS is made, even if the child was cleared for hearing loss in a routine infant or school hearing screening program. If hearing is determined to be within normal limits, parents and caretakers should be alerted to the possibility of hearing loss later in life, and specific plans should be made for regular audiologic monitoring.

When sensorineural hearing loss is identified in a child with TS, ongoing audiologic management is essential. Furthermore, the potentially harmful social and developmental implications of impaired hearing must be considered apart from medical management. The authors have observed children with known syndromes or medical conditions that are managed well in diagnosis and medical treatment but less aggressively with regard to hearing aid use and other rehabilitative efforts. Girls with TS are clearly at increased risk for both conductive hearing loss (Fig. 3) and sensorineural hearing loss, either of which alone or in combination may have significant developmental and communicative consequences. Because children with TS often experience psychoeducational delays even when hearing is normal, it is difficult to determine the added impact of hearing loss. In KC's case, the loss was identified 7 years before the diagnosis of TS. Even then, hearing aid fitting did not occur until the age of 14 years. It is possible that KC's apparent psychosocial difficulties might have been reduced by earlier hearing aid use or that her academic performance might have been facilitated by the use of FM or other assistive technologies.

In summary, TS is a relatively common syndrome with a high incidence of middle ear disease and sensory dysfunction resulting in conductive, sensorineural, and mixed hearing loss. Although the sensorineural component is often described as having onset in later childhood or adolescence, hearing loss may be present at birth or in the preschool years, as illustrated in this case. The natural history of hearing loss in TS is highly variable, but in many individuals, there is a sensorineural hearing loss with a characteristic trough-shaped audiogram and high likelihood of progression. Abnormal hearing sensitivity may appear in the ultra-high-audiometric frequencies before hearing loss is evident from routine audiometric assessment.



**Figure 3** Pure-tone audiogram for a 3-year-old girl with Turner syndrome and a history of recurrent otitis media. ○ = right ear, air-conduction threshold; × = left ear, air-conduction threshold; □ = left ear, air-conduction threshold (masked); [ ] = bone conduction thresholds (masked), recorded from the right and left mastoid, respectively.

Higher order auditory processing has not been systematically investigated, but there is evidence of central auditory dysfunction as well.

The audiologist must be aware of early diagnostic signs since hearing loss may be evident before TS is diagnosed. Whenever a diagnosis of TS is made, audiologic assessment should be provided even if a child has passed a routine infant or school screening. When permanent hearing loss is identified, careful monitoring should be accompanied by early intervention, including the timely fitting of hearing aids and other appropriate assistive devices. Considering the increased risk of social and psychoeducational dysfunction in addition to hearing loss, early and ongoing aggressive audiologic management of this population is essential.

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