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Electrical Status Epilepticus in Slow Wave Sleep: Prospective Case Study of a Cortical Hearing Impairment

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Abstract

The development of a central hearing impairment is described in a young girl with risk factors for hearing impairment that included mosaic Down syndrome, leukemia, and chemotherapy. This case is unusual in the prospective regularity with which hearing was assessed from birth. The diagnosis is electrical status epilepticus in slow wave sleep, a rare childhood disorder, which was associated with lack of responsiveness to auditory signals, regression of emerging speech and language and other cognitive skills, and abnormal electroencephalographic (EEG) activity in both hemispheres. Treatment of the disorder with anticonvulsant medications and steroids has ameliorated the condition by suppressing the abnormal EEG activity and allowing substantial improvements in cognitive and social skills, although communication skills are improving more slowly.

Key Words: Auditory evoked potentials, central, Down syndrome, hearing impairment, hearing loss

Abbreviations: ABR = auditory brainstem response, CPA = conditioned play audiometry, CSWS = continuous spikes and waves during slow wave sleep, EEG = electroencephalography, ESES = electrical status epilepticus of slow wave sleep, LKS = Landau-Kleffner syndrome, MRI = magnetic resonance imaging, MRL = minimal response level, REM = rapid eye movement, TEOAEs = transient evoked otoacoustic emissions, VRA = visual reinforcement audiometry

The following case study describes an uncommon auditory disorder of sudden onset, with multiple complicating issues. The child had a complex history, which required the cooperative interaction of a number of disciplines to achieve an accurate diagnosis of the cause for the hearing disorder. The case concerns a 2½-year-old child, ER, who was born to young, educated parents. At the time that her hearing impairment was detected, she was being followed in an audiology clinic with a diagnosis of Down syndrome and leukemia, which was in remission. Unlike most other cases, ER's hearing has been well documented prior to, during, and subsequent to the development of her hearing impairment.

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CASE HISTORY

ER was born in May 1995 with mosaic Down syndrome (trisomy 21), although she was virtually without physical stigmata. She was born 2½ weeks prematurely and weighed 5 pounds, 5 oz. When she was 3½ weeks of age, her parents reported that she looked pale and bruised. Subsequent evaluation revealed hepatosplenomegaly and respiratory distress, resulting in a diagnosis of acute lymphocytic leukemia. She remained hospitalized for 8 weeks and was brought into remission with chemotherapy. For the next 2 years, she was reported to be thriving and making good developmental gains. During this time, she was seen weekly for early intervention services. In the late summer

of 1997, her parents and an early intervention specialist observed sudden changes in her auditory behavior and suspected that she had a hearing impairment.

ER has been followed with hearing evaluations every 6 months since birth because the Down syndrome put her at risk for hearing impairment. The high prevalence of hearing impairment in persons with Down syndrome is well documented (Fulton and Lloyd, 1968; Brooks et al, 1972; Balkany et al, 1979; Dahle and McCollister, 1986; Roizen et al, 1993; Diefendorf et al, 1995; Kile, 1996), although the prevalence of hearing loss in persons with the mosaic form of Down syndrome is not well documented. Down syndrome is associated with several types of hearing loss, but the most common type of loss is conductive (Dahle and McCollister, 1986). Although studies of the prevalence of hearing loss have varied, it has been reported that approximately 75 percent of individuals with Down syndrome have conductive hearing losses that include cerumen impaction from stenotic ear canals, otitis media from poor eustachian tube function, malformation of the nasopharynx, hypotonia, and high susceptibility to upper respiratory infections (Dahle and McCollister, 1986; Jung, 1989). Even when no conductive pathology is present, children with Down syndrome typically have thresholds that are 10 to 25 dB worse than those of their nonaffected peers (Widen et al, 1987; Kile, 1996; Werner et al, 1996). Sensorineural hearing loss, attributed to shortened cochleas and a reduced number of fibers in the cochlear nucleus, also occurs in 10 to 15 percent of cases (Jung, 1989).

The history of this child is complicated by the early episode of leukemia. Leukemia occurs with a higher incidence in children with Down syndrome than in unaffected children (Zipursky et al, 1992). Leukemia has been associated with both conductive and sensorineural hearing impairment primarily through infiltration of the temporal bone, resulting in hemorrhage and degenerative changes in the middle ear and cochlea or through infiltration of the auditory nerve (Schuknecht et al, 1965; Paparella et al, 1973; Schuknecht, 1993). Although much of the hearing loss in leukemia may result from secondary infections and chemotherapy (Schuknecht, 1993), sudden hearing loss has been documented as a presenting symptom of leukemia. Severe to profound, bilateral, sensorineural hearing loss of sudden onset was reported as an initial symptom of acute lymphocytic leukemia (Veling et al, 1999) and of chronic myelogenous leukemia (Genden and Bahadori, 1995; Shaar and Singletary, 1999). This complication of leukemia is considered to be rare (Genden and Bahadori, 1995).

Leukemia is treated with powerful chemotherapeutic agents, which may have significant side effects. ER was treated with ara-C (cytosine arabinoside or cytarabine), idarubicin, etopside (VP-16), and dexamethasone. There are many side effects of each of these medications, including effects that may be significant to the sensory and neural systems. Ara-C may be associated with neural toxicity, seizures, cerebral and/or cerebellar dysfunction (Baker et al, 1991), and headache and dizziness (*Physicians Desk Reference* [*PDR*], 2000), although these are not among the most common side effects (*PDR*, 2000). Idarubicin used with ara-C may be associated with headaches (20%), peripheral nerve damage (7%), seizures (4%), and cerebellar dysfunction (4%) (*PDR*, 2000). Previously, etopside has been associated with dizziness, transient cortical blindness, optic neuritis, and peripheral neurotoxicity (*PDR*, 1999), but, currently, the only neurologic side effect listed is peripheral neurotoxicity in 1 to 2 percent of cases (*PDR*, 2000). Dexamethasone may be associated with convulsions, increased cranial pressure, vertigo, and headaches (*PDR*, 2000), although these side effects are sufficiently rare that they have not been seen in 19 years of experience in pediatric neurology by one of the authors (KEH). None of these drugs has been evaluated for safety in infants and children.

Audiologic Evaluations

One of the unique aspects of this report is the prospective regularity with which auditory function was evaluated. Because of the ongoing risk of hearing loss associated with Down syndrome, ER was scheduled to have an audiologic evaluation every 6 months. She was tested with visual reinforcement audiometry (VRA) in the sound field for all evaluations through May 1999, but her latest two evaluations, which were done with conditioned play audiometry (CPA), and individual ear thresholds were obtained. The results of these evaluations, with comments regarding her behavior to auditory signals, are shown in Table 1. Minimal response levels (MRLs) for speech and the multitone complex (500–2000 Hz) for all of the evaluations are shown in Figure 1. Tympanometry showed normal middle ear pressures and normal peak height (ASHA, 1990) on all evaluations.

Table 1 Minimum Response Levels (in dB HL) for Signals (Tonal Signals, Speech, and Multitone Complex in Sound Field with Visual Reinforcement Audiometry (Except as Noted), Other Tests, and Observations of Auditory Behavior

	Frequency (Hz)							
Date	*250*	*500*	*1000*	*2000*	*4000*	*Speech*	*MTC*	*Other Tests/Observations*
5/96	20	20	20	20	15	15	15	Auditorily alert Natural head turns to sound source Good response consistency and latency
11/96	15	15	15	15	15	15	10	No change in auditory behavior Some adaptation to auditory signals Vocalizing, imitating speech
5/97	30	25	15	15	20	15	15	Subtle regression in auditory behavior Some inconsistent and delayed responses Increased adaptation to auditory signals Says few single words and imitates sound
10/97	CNT	CNT	CNT	CNT	CNT	55	50	Dramatic changes in auditory behavior Lacked auditory alertness Delayed responses, "tuning out" behavior Mother, teachers, and therapists suspected hearing impairment Regression of speech and language Normal TEOAEs
11/97	CNT	CNT	CNT	CNT	CNT	40	40	Could not be brought to task Difficulty localizing sounds No longer speaking or imitating sounds Pocket talker introduced with benefit Learning sign language Normal TEOAEs
2/98	DNT	90	85	75	DNT	70	DNT	No change in auditory behavior Normal TEOAEs and ABR
4/98	CNT	CNT	CNT	CNT	CNT	35	45	Not very visually alert No meaningful speech but has about 10 signs Some aggressive behavior Normal TEOAEs
11/98	CNT	CNT	CNT	CNT	CNT	15	20	Improvements in auditory behavior Appropriate response latencies Short intervals of on-task behavior Fewer aggressive episodes Vocalizing and imitating speech
5/99	CNT	CNT	CNT	CNT	CNT	10	20	Increased vocalizations Appropriate response latencies Localizes well to both sides Less adaptation to auditory signals Improved eye contact and social behavior Produces some words with prompting
11/99	CNT	CNT	CNT	CNT	CNT	R5* L10*	15	Improved auditory behavior but not to 1996 level No "tuning-out" behavior Increased vocalizations with some word approximations Localizes speech well to both sides No longer acts hearing impaired Good social interactions
5/00	DNT	R15* L15*	R10* L10*	R10* L10*	R10* L10*	R5* L5*	DNT	Exhibited compliant, interactive behavior Good response consistency and latencies Pure-tone threshold testing with CPA Has a few word approximations and about 6 signs Continues to favor visual learning

*Conditioned play audiometry with earphones.

MTC = multitone complex (500, 1000, 2000 Hz), CNT = could not test due to inconsistent responses, DNT = did not test, R = right ear, L = left ear.

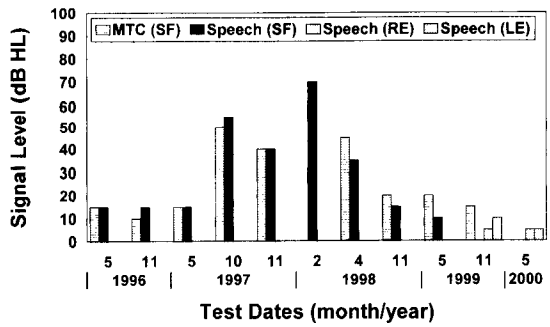

Figure 1 Minimum response levels for speech detection and a tone complex (MTC) (500, 1000, 2000 Hz) for each of the audiologic evaluations from May 1996 until May 2000. All evaluations were in the sound field (SF) by visual reinforcement audiometry except for the speech detection in the last two evaluations, which were under earphones by conditioned play audiometry

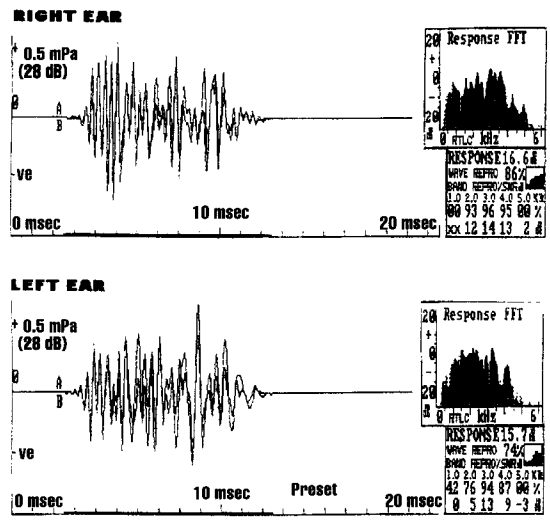

Figure 2 Results of the transient evoked otoacoustic emission tests (TEOAEs) obtained in October 1997. TEOAEs were present from 2000 to 4000 Hz bilaterally to clicks at 82 dB pSPL.

In November 1995, ER's initial evaluation was at the age of 6 months, when she was tested with an auditory brainstem response (ABR). This evaluation indicated normal, bilaterally equal central conduction times, with click thresholds suggesting no worse than a mild hearing impairment in both ears.

In May and November 1996, during the earliest behavioral evaluations, there were no concerns regarding ER's hearing. MRLs to speech, frequency-specific stimuli (warble tones and critical-band noise), and the multitone complex (500–2000 Hz) were between 10 and 20 dB HL for the first two evaluations. These levels are consistent with "best hearing" for children with Down syndrome (Kile, 1996). During these evaluations, ER exhibited auditory alertness, good response consistency, and appropriate response latencies and localized well to the sound source when sound was presented from both the right and left sides. She was reported to be healthy, thriving, and making good developmental gains. At 1½ years of age, ER was vocalizing frequently and imitating speech.

In May 1997, results of the audiologic evaluation suggested little change in ER's hearing sensitivity compared with previous evaluations, but subtle changes were noted in her auditory behavior. For the first time, ER demonstrated some response inconsistencies, delays, and auditory adaptation and was easily distracted from the auditory task. In retrospect, these behaviors may have been the initial signs of her developing difficulties in processing auditory signals. The results indicated a possible mild low-frequency hearing loss. Although she had had two episodes of otitis media in the previous 6 months, on this date, her tympanograms were normal.

In late September 1997, there were increasing indications of a problem with ER's hearing. The early intervention specialist and speech and language pathologist indicated that ER was acting as a child with a hearing impairment and had shown significant regression in her speech and language, having lost her 20-word vocabulary. The mother reported that ER's auditory behavior deteriorated in July, and she was concerned about the child's hearing. There was no change in health associated with the behavioral changes. When ER had her audiologic evaluation in early October, MRLs for speech and the multitone complex were consistent with a moderate hearing impairment. ER did not respond consistently to frequency-specific signals (warble tones and critical-band noise). Transient evoked otoacoustic emissions (TEOAEs) were tested for the first time and were present at normal amplitudes (Fig. 2). Management suggestions included getting ER's attention with visual and/or tactile cues before speaking to her, using short sentences, giving her time to respond, and periodically checking for auditory comprehension. It was recommended that ER's early intervention program include the services of an educational audiologist and a teacher of the hearing impaired and that ER be introduced to amplification with a pocket talker following medical clearance. ER was referred to her pediatrician, who ordered a magnetic resonance imaging (MRI) study.

By the end of October 1997, the mother reported that ER's hearing was fluctuating, but she was still unable to localize a sound source. The results of the MRI suggested "no evidence of any abnormality of the cerebellopontine angle or internal auditory canals." When ER was evaluated in November, there were increasing signs of a serious hearing impairment. A report from the early intervention specialist indicated that ER was not alert to auditory signals, and she no longer imitated speech accurately. She was visually alert and responded to tactile stimuli. In ER's early intervention program, the educational audiologist introduced her to a pocket talker, which resulted in some improvement in her responses to auditory signals. She was also seen by a teacher of the hearing impaired and began learning sign language. Results of the audiologic evaluation were again suggestive of a mild to moderate hearing impairment with MRLs that were slightly better than on the previous evaluation. Again, ER was not responsive to frequency-specific signals, but TEOAEs were present in both ears. During the evaluation, her responses were inconsistent, and she exhibited some "tuning out behaviors." ER was not alert to auditory signals and had difficulty localizing the sound source. ER was referred for a diagnostic and threshold ABR to confirm thresholds and to rule out pathology of the eighth nerve and auditory brainstem pathways.

In February 1998, ER was referred to the University of Wisconsin Clinical Science Center for a medical evaluation by a pediatric otologist and clearance for anesthesia for the ABR. A second MRI was ordered. A behavioral test prior to the ABR produced MRLs to speech and narrowband noise in the moderately severe to severe range. TEOAEs were present. A sedated ABR with click stimuli elicited bilaterally symmetric responses with absolute and interwave latencies that were within normal limits (Fig. 3). The wave V thresholds were at 15 dB HL for clicks (Fig. 4) and better than 45 dB nHL for tone pips at 500 and 1000 Hz. The MRI was read as negative, and, again, no medical explanation for her hearing loss was found.

On a follow-up examination in April 1998, the results of behavioral testing (VRA) continued to suggest a mild to moderate hearing loss, and ER again did not respond consistently to tonal signals. Again, TEOAEs were normal. No changes in auditory behavior were observed in comparison with the previous evaluation. She had lost all meaningful speech and was beginning to display episodes of aggressive behavior. ER was referred to a pediatric neurologist.

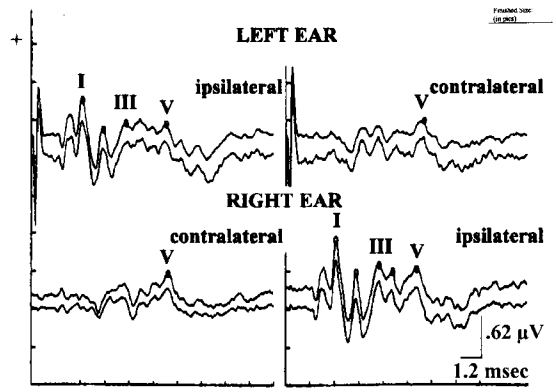

Figure 3 Waveforms from the auditory brainstem evoked response testing of February 1998, which show responses from the left ear (ipsilateral response at the top left and contralateral response at the top right) and the right ear (contralateral response at the bottom left and ipsilateral response at the bottom right). Absolute wave latencies and interwave intervals were within normal limits bilaterally. Stimuli were clicks at 90 dB nHL presented at a rate of 7.7/msec through insert earphones.

In July 1998, ER had a complete neurologic examination. It was noted that within the first few weeks of life, ER did not use her left hand frequently, and she was clearly right handed by the age of 3 months. ER had been experiencing sleep disturbances since her communication skills had regressed. A sleep study that included an overnight electroencephalogram (EEG) was done. Results of the EEG were consistent with a diagnosis of electrical status epilepticus of slow wave sleep (ESES). ER was started on a course of steroids (prednisone), anticonvulsants (valproic acid), and ranitidine. After she had been on medication for a week,

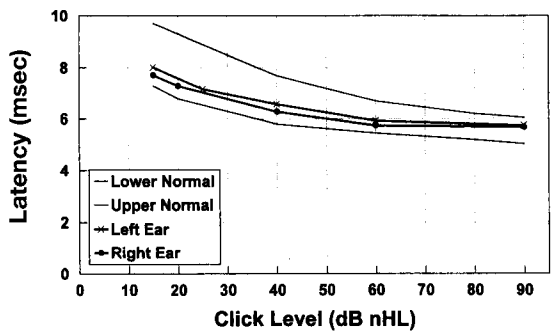

Figure 4 Latency-level function for wave V for both ears for ER (x = left ear and o = right ear) plotted against the normal range. All wave V latencies and the click threshold were within normal limits. Click level (dB nHL) is on the abscissa and latency (msec) is on the ordinate.

some improvements were noted, including increasing vocalizations and improved ability in sound localization but no improvement in speech production. She was on the maximum dosage of steroids for 1 month, and the dose was tapered off for the next 6 weeks.

In September 1998, a follow-up neurology appointment indicated that ER's regression in skills had been halted. Her mother reported that there were significant improvements in ER's social behavior, eye contact, and sleep patterns, although her communication skills had not returned to 1996 baseline levels. A waking EEG indicated that the abnormal left hemispheric spike and slow wave activity had been halted, but abnormalities continued in the right temporoparietal regions. It was hypothesized that early in life, ER suffered right hemispheric damage that became the primary focus of seizure activity and resulted in a very mild left hemiparesis. Once both hemispheres became engaged in the abnormal electrical activity, ER's regression of skills began. The medications were ameliorating the situation, but a resistant area remained in the right cerebral hemisphere in the distribution of the middle cerebral artery. The valproic acid was increased, and ER's condition continued to be monitored.

In November 1998, ER had her first hearing evaluation after beginning treatment. On this date, substantial improvements were observed in her auditory behavior, and, again, MRLs to speech and the multitone complex were consistent with "best hearing" for children with Down syndrome. ER's responses to tonal signals continued to be unreliable. Her mother reported that ER was more responsive to sound and was vocalizing and mimicking more but still had no meaningful speech. In addition, ER was becoming more social and was having fewer episodes of aggressive behavior. She was taking valproic acid and was soon to begin phenytoin as well.

The abnormal EEGs continued for several months. In February 1999, an overnight EEG continued to show spike activity, but, by April, a 24-hour EEG indicated little spike activity. ER continued to take the valproic acid and phenytoin. At her May audiologic evaluation, ER was active, vocal, and alert. Her MRLs to speech and the multitone complex were within normal levels, although she continued to exhibit inconsistent responses to frequency-specific signals. Although she demonstrated some adaptation to auditory signals, she could generally be brought to task with increases in sound level. She localized well to the sound source.

ER's next audiologic evaluation was in November 1999. ER's mother reported that ER had a positron emission tomographic scan in October, which revealed no seizure activity. Phenytoin was discontinued, but she continued taking valproic acid. For the first time, ER responded to sound using CPA. Normal speech detection thresholds for each ear were obtained under earphones, and a normal threshold for the multitone complex was obtained in the sound field. Again, she did not respond consistently to frequency-specific signals. Her auditory behavior had significantly improved since her treatment but had not yet reached the levels noted in evaluations of 1996. She had increased vocalizations and some word approximations, and social behavior was no longer problematic.

ER's latest audiologic evaluation was in May 2000. Her mother reported that ER recently discontinued the valproic acid, which was described as suppressing but not eliminating the abnormal EEG activity. Her behavior has not changed with the removal of all medications. She is scheduled for a magnetoencephalogram in order to define precisely the limits of the cortical area giving rise to the abnormal activity. If this area can be determined, she will be considered as a candidate for surgical isolation of that area. During the audiologic evaluation, for the first time, CPA was used to obtain monaural thresholds to speech and pure-tone thresholds that were within normal limits for both ears. ER was compliant and interactive throughout the session and was easily brought back to task when her attention wandered. She has a few words and a few signs and continues to work on sign language. She is learning the Picture Exchange Communication System. Despite the fact that ER's hearing and auditory behavior were generally within normal limits, her mother reports that ER continues to be a visual learner.

DISCUSSION

ESES, sometimes called continuous spikes and waves during slow wave sleep (CSWS), is a rare childhood disorder that is characterized by a specific EEG pattern of continuous spike and slow wave activity during nonrapid eye movement (non-REM) sleep (Jayakar and Seshia, 1991). The disorder was described initially by Patry et al (1971), who characterized the disorder as requiring the abnormal EEG activity to occur 85 percent of the time during sleep. The EEG abnormalities also may occur during waking hours and produce seizures. If

the abnormalities occur only during sleep, overt seizures are not present, and the disorder may not be recognized for years (De Negri, 1997). Behavioral symptoms of the disorder include sleep disturbances, behavioral problems, and regression of speech and language, all of which may fluctuate over time (Deonna and Roulet, 1995). ER had the characteristic spike activity over both hemispheres. She experienced regression of her emerging speech and language, displayed aggressive tendencies, and avoided making eye contact. This constellation of symptoms was suggestive of "autistic regression," acquired aphasia, or central hearing impairment. Although she had sleep disturbances, she had no overt seizures.

The differential diagnosis of ESES includes Landau-Kleffner syndrome (LKS), which is sometimes called acquired childhood aphasia with convulsive disorder. This disorder was originally described by Landau and Kleffner (1957) and includes symptoms of interruption of normal speech and language development, epileptic activity, and severe paroxysmal EEG activity. The abnormal EEG activity can persist in REM sleep and during waking (De Negri, 1997). The two disorders may overlap, and some believe that they are similar enough to be manifestations of the same underlying disorder (Roulet et al, 1991; De Negri, 1997; Gordon, 1997; Rossi et al, 1999). Rossi et al (1999) observed several patients whose EEG records over time included patterns from both ESES and LKS. The diagnosis of LKS is based on clinical symptomatology (Bureau, 1995). Morrell (1995) insists that LKS can exist only in a child who previously displayed normal speech and language development.

The audiometric profile, in this case, involves a fluctuating hearing impairment of cortical origin. Especially when the disorder begins at an early age in a patient, the hearing impairment may be confused with a loss of peripheral origin (Deonna and Roulet, 1995). In keeping with the cortical site of origin for the hearing impairment, tympanograms, acoustic reflexes, and OAEs were normal, and ABRs exhibited latencies that were within normal limits, as well as wave V thresholds that were within normal ranges. There was no indication of brainstem involvement, which is consistent with the report of electrophysiologic testing on two cases by Co et al (1985).

The cause of ESES is unknown. Most cases have no identified lesion by computed tomography or MRI, although some cases are associated with trauma or lesions. It is thought that the abnormal electrical activity in the temporal and parietal cortex disrupts emerging speech and language functions, and, if it lasts long enough, subsequent development will also be compromised (Gordon, 1997). It is not known what role, if any, the Down syndrome, leukemia, and chemotherapy had on the onset of the ESES. Seizure disorders are modestly more prevalent in the population having Down syndrome than in the normal population (Guerrini et al, 1990; Pueschel et al, 1991), but ESES has not been reported in individuals with Down syndrome. In ER's case, the most likely cause is the early treatment with chemotherapy, but this cause cannot be substantiated.

The treatment for ESES is variable because individual patients react differently to treatment regimens. The medical treatment typically includes anticonvulsant drugs to control the seizure activity. Anticonvulsant drugs typically have no effect on the aphasia even when the epileptic activity is controlled (Deonna and Roulet, 1995). Steroids in conjunction with the anticonvulsants are often beneficial. Occasionally, if the epileptic area is focal, surgery may be used to isolate that area to prevent the spread of epileptic activity (Gordon, 1997). Speech therapy is also recommended. ER had been involved in an early intervention program, speech therapy, and physical therapy since soon after birth because of her Down syndrome.

The prognoses for remediation of the abnormal EEG activity and for the aphasia are separate. The abnormal EEG activity and seizures typically end in adolescence (Dugas et al, 1995), whereas the outcome for the aphasia is more variable. Several factors contribute to a more favorable outcome for the aphasia. Prognosis is worse if the abnormal EEG persists over time (van Dongen et al, 1995). Prognosis is better if only one hemisphere is involved, although, typically, both hemispheres are involved. More favorable prognosis is also suggested if the disorder is caught early and treated aggressively and if the child has already passed sensitive periods for development, such as those for the development of speech and language, prior to the onset of the disorder (De Negri, 1995). Relative to ER, prognosis is guarded. Both hemispheres were involved. Diagnosis was perhaps a year after the initial symptoms, which, according to the literature, is not unusually long. In the case of ER, the symptoms were fluctuating. Her symptoms began at age 2½ years, just as she was beginning to develop speech and language,

and speech and language were already somewhat delayed given the presence of the Down syndrome.

The course of this disorder is also variable. Some children recover fully and others experience relapses, but most suffer irreversible disruptions of their cognitive development. Remissions are reported to occur both with and without the anticonvulsants and steroids (van Dongen et al, 1995), although few documented cases are left untreated. During adolescence, the abnormal EEG pattern and the epileptic seizures decline in frequency, and neuropsychological function may improve. Most of the cases reported in the literature, however, indicate that most children do not recover full cognitive or linguistic skills (Jayakar and Seshia, 1991). ER continues to be followed by neurology and has audiologic evaluations at 6-month intervals.

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