

Hearing Loss and Congenital Symptomatic Cytomegalovirus Infection: A Case Report of Multidisciplinary Longitudinal Assessment and Intervention

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Abstract

More than 6000 children born annually in this country have hearing loss resulting from congenital cytomegalovirus (CMV) infection, the leading nonhereditary congenital cause of hearing loss in children. This exemplary congenital symptomatic CMV case focuses on the results of longitudinal audiologic, educational, medical, psychological, and visual evaluations and intervention. Decreased ocular motor control and visual acuity were observed as was bilateral deterioration of hearing from 3 days through 9 years of age. Treatment with dexamethasone and histamine resulted in almost complete reversal of the most recent progression of hearing loss in the left ear.

Key Words: Congenital cytomegalovirus (CMV) infection, hearing loss, immunosuppressant agents, multidisciplinary longitudinal assessment

The congenital cytomegalovirus (CMV) infection rate ranges from 0.5 to 2.4 percent (Starr et al, 1970; Hanshaw, 1971; Stagno et al, 1977; MacDonald and Tobin, 1978), with an average infection rate of 1 percent of all live births (U.S. National Center for Health Statistics, 1991). CMV is not only the most frequent congenital infection in humans, but is also the leading congenital nonhereditary cause of sensorineural hearing loss in children (Hanshaw, 1982; Hicks et al, 1993). Results from a study by S. Harris and colleagues (1984) suggest that congenital CMV is the single leading cause of childhood sensorineural hearing loss. Nonetheless,

CMV hearing loss has been difficult to characterize because of differences in research protocols, subject groups, and individual subjects. From 1964, when Medearis first described the symptoms associated with CMV, reports suggest that about 60 percent of subjects with the CMV symptom complex, including hepatosplenomegaly, microcephaly, thrombocytopenia, and jaundice with direct hyperbilirubinemia, have hearing loss (Hanshaw, 1971; Stagno et al, 1977; Saigal et al, 1982; Bopanna et al, 1992). Additionally, congenital asymptomatic CMV, which occurs in over 90 percent of newborns with CMV infection, causes hearing loss over several years in as many as 15 percent of cases (Williamson et al, 1992). When these percentages are combined and applied to the annual birth rate of 4.1 million in the United States, more than 6000 children born each year experience sensorineural hearing loss as a result of congenital CMV infection (Hanshaw et al, 1976; Stagno et al, 1977; Saigal et al, 1982; Williamson et al, 1990, 1992; Bopanna et al, 1992). Hearing

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loss continues to worsen or occurs later in life in approximately 75 to 80 percent of these subjects (Dahle et al, 1979; Stagno, 1990; Williamson et al, 1992).

Although treatment protocols for progressive or idiopathic sudden deafness frequently involve steroids (Wilson, 1980, 1986; Hall et al, 1993), treatment of CMV in humans has generally involved antiviral drugs rather than immune response-mediating drug therapies, and the antiviral drugs are usually not prescribed as a specific treatment for deafness (Reigstad et al, 1992; Attard-Montalto et al, 1993; Trang et al, 1993). Further, outcome studies of CMV treatment with antiviral drugs such as ganciclovir have not reported hearing loss reversal or hearing improvement in humans (Demmler, 1991). However, studies involving guinea pigs (GPCMV) have suggested that the CMV damage to the auditory system may be partially immune-mediated (Harris et al, 1990). These studies have demonstrated that administration of cyclophosphamide for a 13-day period resulted in better preserved hearing, with experimental animals showing moderate hearing loss as opposed to profound hearing loss in the untreated control group (Darmstadt et al, 1990).

This case report summarizes multidisciplinary longitudinal evaluations and intervention data from the first decade of life of a subject with hearing loss and congenital symptomatic CMV infection. The subject, followed by the Perinatal Infectious Disease Project at The University of Alabama at Birmingham, was selected from a cohort of 78 subjects with hearing loss and congenital CMV infection. The report also describes treatment of hearing loss progression and subsequent improvement in hearing sensitivity.

CASE REPORT

The female subject was the product of a term pregnancy for a healthy, white 19-year-old with no pregnancy complications other than an upper respiratory infection with low-grade fever for 1 day during the fourth to fifth month of pregnancy. The subject had symptomatic manifestations of CMV in the neonatal nursery: facial petechiae, thrombocytopenia, hepatosplenomegaly, and jaundice with direct hyperbilirubinemia. A urine culture for CMV was positive. Meconium aspiration resulted in lung disease and supplemental oxygen was required. Hearing evaluation using auditory brainstem response (ABR) click stimuli was conducted at 3 days of age. Replicated waveforms at 20 dB nHL

suggested normal hearing for each ear in the higher frequency range (1000–4000 Hz). When examined initially at 1 month of age by the project pediatrician, the subject was small, but alert and attentive. No petechiae were detected at this time; the platelet count had increased, but was still below normal, and hepatosplenomegaly was evident. By 7 months of age, the platelet count was normal and hepatosplenomegaly was no longer present. At the 1-year evaluation, the pediatrician noted that physical development was appropriate with the exception of increased muscle tone in the lower extremities, with toes often held in an abnormal position. The subject's mother was concerned that the child had been delayed in sitting independently and was not walking without assistance. Results of the Alpern Boll Developmental Profile (Alpern et al, 1980) administered at the 1-year evaluation suggested normal intelligence, delayed motor development, and delayed communication development.

Psychological evaluation at 4 years, 2 months of age using the Leiter International Performance Scale (Arthur, 1952) revealed normal intellectual functioning. However, a developmental profile (Alpern et al, 1980) administered at the same time showed an 8-month delay in both motor and academic development and a 14-month delay in communication development. Psychological assessment at 7 years, 8 months of age indicated normal intellectual functioning. Achievement test scores indicated reading skills commensurate with IQ; however, arithmetic skill deficiencies were noted. Adequate motor speed was noted, but fine motor coordination was poor on the left side. Behavioral assessment revealed no significant problems. Visual perceptual skills had improved and, at the time of this testing, were within the expected range. Results of the Alpern Boll Developmental Profile (Alpern et al, 1980) showed motor development at 3 months above normal, academic development 5 months delayed, and communication development 21 months delayed. At 9 years of age, according to her teachers, the subject's math and reading performance was at grade level.

Vision examination at 2 months indicated that the pupils were sluggishly reactive to light and that low hyperopia was present in each eye. Exotropia of the left eye at close range only was detected at age 4 years, 9 months. Because of alternating exotropia, home eye exercises were initiated at 5 years, 3 months of age. Visual acuity at that time was 20/20 for both distant and near ranges. At 6 years, 5 months of age, constant

left exotropia at distance and intermittent left exotropia at close range with poor ability to fuse were reported. Visual acuity was 20/25+ for each eye tested separately and 20/20 for both eyes tested simultaneously. The subject was fitted with eyeglasses at this time. At 8 years, 10 months of age, an increased amount of alternating exotropia and decreased visual acuity to 20/30+ aided were detected in each eye, and, at this time, the prescription strength of the subject's eyeglasses was increased.

Hearing

Serial audiologic evaluations (N = 35) performed from the age of 3 days, when hearing was normal, through 9 years provided documentation of prolonged bilateral deterioration of hearing (see Fig. 1). At the age of 2 months, air- and bone-conduction ABR results indicated mild bilateral sensorineural hearing loss. At approximately 4 months of age, ABR click test results for air and bone conduction were consistent with bilateral sensorineural hearing loss: mild to moderate in the left ear and profound in the right ear. At 6 months of age, the subject was fitted with a hearing aid in the left ear. During the next several months, she experienced numerous episodes of otitis media. Behavioral results obtained in sound field for the better ear (left) indicated hearing loss fluctuations between moderate and severe. The subject continued to have bouts of otitis media and was referred to an otolaryngologist, who inserted pressure equalization tubes at 1 year of age. Behavioral test results obtained in sound field following insertion of the tubes suggested moderate sensorineural loss of hearing. The subject was fitted with bin-aural aids at that time.

From 2 until 7 years of age, hearing loss was relatively stable bilaterally: profound in the right ear and moderate in the left ear. At 7 years of age, hearing loss increased to the severe range in the left ear.

At 8 years and 4 months of age, the subject complained that her hearing aid and auditory trainer were broken. Her teachers and parents certified that those amplification devices were functioning appropriately; however, the patient continued to complain of poor hearing and a constant fluttering sensation in the left ear. Her demeanor changed from happy and compliant to anxious. She was referred to her pediatrician, who diagnosed bilateral effusion with a mild infection in the left ear; an antibiotic and a decongestant were prescribed.

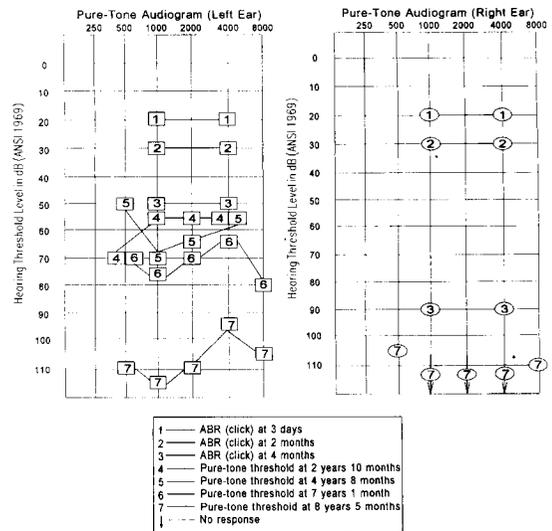


Figure 1 Audiologic results documenting bilateral progression of sensorineural hearing loss in a child with symptomatic congenital CMV infection.

Ten days later, the subject complained of complete deafness in her left ear and of the continued fluttering sensation in that ear. When examined by an otolaryngologist, no evidence of middle ear fluid or infection was seen. Audiologic results confirmed that hearing had decreased to a profound loss in the left ear. The subject was hospitalized and received a CAT scan, which revealed no abnormalities. Intravenous histamine and dexamethasone were initiated and continued for 3 days. Upon dismissal from the hospital, audiologic test results continued to show bilateral profound loss of hearing. The subject began a regimen of oral dexamethasone (2 mg twice a day), histamine sublingual drops, cyclandelate tablets, and cimetidine. After 5 days, the subject reported better hearing in her left ear, and periodic audiologic monitoring documented gradual improvement in hearing sensitivity, as shown in Figure 2. Two weeks following initiation of medication, a 15 to 25-dB improvement in hearing thresholds for the 0.5- to 8-kHz range for the left ear was documented and the dosage of dexamethasone was decreased to 2 mg once a day for 1 week and then to 1 mg once a day for 1 week. The subject experienced weight gain and moodiness as a consequence of medication, so the dosage was further tapered to 0.5 mg every other day, with continued use of histamine drops. The subject's mother reported that the child's former personality and happy temperament had returned, though she

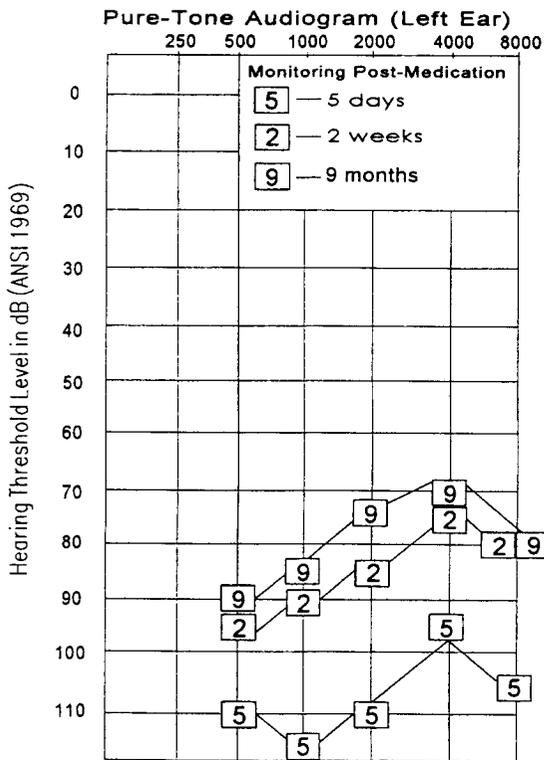


Figure 2 Audiologic results documenting improvement in sensorineural hearing loss in the left ear following medication.

experienced facial puffiness. The fluttering sensation in her left ear was no longer present. Dexamethasone was discontinued after 2½ months. Audiologic testing at 9 months from initial treatment revealed continuing substantial improvement in hearing without any medications. Audiologic results obtained at 16 months from initial treatment indicated stable levels despite some reported subjective fluctuations in hearing.

DISCUSSION

Studies have suggested that the pathologies causing hearing to deteriorate in CMV-infected inner ears include both the host's inflammatory response and the cytopathic effect of the virus (Keithley et al, 1989). Stagno and colleagues (1977) speculated that immune-mediated damage, including inflammation and edema of inner ear structures, might be as important or more important than viral damage. GPCMV studies lend further support to immune-mediated damage (Harris et al, 1984; Woolf et al, 1985). Of additional importance in GPCMV study is that viral reactivation did not occur with the use of the immunosuppressant cyclo-

phosphamide. It appears also that cyclophosphamide can reach inflammatory cell infiltrates in inner ear structures. Darmstadt and colleagues (1990) speculated that because cyclophosphamide and prednisone are efficacious in other autoimmune disorders, their use in sensorineural hearing loss of viral origin could be appropriate. The antiviral agent ganciclovir, a virostatic drug that does not kill or otherwise eliminate CMV, but holds it in check until the drug is stopped, also has been proposed (Woolf et al, 1988). The drug has been approved for adult use, and trials with newborns have begun (Demmler, 1991).

Treating viral-related illnesses with immunosuppressant agents (ISAs) is not innovative. Infectious mononucleosis (Epstein-Barr virus), Bell's Palsy (herpes simplex virus), and Ramsay-Hunt syndrome (varicella zoster virus) are all examples of viral-mediated illnesses that respond to steroids. Theoretically, with any of these viruses, ISAs could cause viral reactivation and spread. Questions still remain regarding the risks of latent or persistent viral disease and side effects when using ISAs; these concerns mandate close monitoring (Keithley et al, 1989). Although treatment variables associated with each case must be assessed carefully, with attention given to possible benefits and particular risks, ISA treatment should be considered for CMV-related delayed onset/progressive sensorineural hearing loss, just as progression of sensorineural hearing loss in non-CMV cases is treated. If the loss is secondary to an autoimmune process, then ISAs should be beneficial. If inflammation can be halted before structural damage occurs, then hearing loss may be prevented. If the risk of viral reactivation is low, then treatment with these agents seems reasonable. It could, in fact, be speculated that, in the chronic situation, ISAs could make viral particles still present more accessible so that antiviral agents can more readily reach them. Combination therapy using antiviral agents with either corticosteroid or cyclophosphamide merits investigation.

As in cases with autoimmune hearing loss, hearing gain can be dramatic during a short period of time or may require months; therefore, treatment should not be discontinued prematurely (McCabe, 1979). There is probably a degree of urgency in initiation of therapy as a loss in hearing of recent onset is more likely to respond than one that occurred months or years earlier (Hicks and Wright, 1991). In this particular case, the most recent progression of sensorineural hearing loss was halted and reversed by the use of ISAs. This patient's hearing was

clearly progressive without therapy and showed dramatic reversal of the recent drop with the use of corticosteroid and vasodilator (dexamethasone and histamine).

Routine screening for congenital CMV, hearing, and vision with multidisciplinary intervention services resulted in improved outcome for this patient. Intervention services were modified to accommodate needs as development and sensory abilities changed. The various educational services for children with hearing loss included a parent-infant program, a correspondence course for parents, a self-contained class, and finally a regular class with total mainstreaming. Audiologic services included early baseline and frequent threshold monitoring, hearing aids with maximum flexibility in power and frequency response, as well as training in communication methods that accommodated changing hearing levels. Training provided to teachers and parents regarding CMV and hearing loss included information about changes in behavior that could indicate deterioration of hearing.

In contrast to the timely identification and intervention for the symptomatic case described, most children born with CMV infection do not have overt symptoms during the first 3 weeks of life and are not identified. Unfortunately, after 3 weeks of age, they cannot be differentiated from the 60 to 80 percent of the general population with postnatally acquired CMV, which is generally inconsequential (Demmler, 1991). Further, these children who acquire CMV postnatally are not known to be at risk for early onset, delayed onset, or progressive hearing loss; vision abnormality; neurologic problems; and/or learning difficulties. These complications of congenital asymptomatic CMV infection are frequently identified late and are usually managed medically and educationally without knowledge of the etiology.

Substantial effort is being put into research for the establishment of an effective universal newborn hearing screening program (National Institutes of Health, 1993) and refinement of the risk criteria for hearing loss (Joint Committee on Infant Hearing, 1991). Successful implementation of these efforts will reduce the average age of identification for many infants who are deaf or hard-of-hearing. However, neither of these efforts will identify the 37,000 infants born annually in this country with congenital asymptomatic CMV infection who are at risk for early onset, delayed onset, and/or progressive hearing loss, as well as other disabling conditions.

Further, those who have or develop hearing loss and are identified later cast doubt as to the validity of hearing screening procedures. Appropriate monitoring at 2- to 6-month intervals for progressive or delayed onset hearing loss in this population is dependent on CMV identification, and this can be accomplished only through screening for CMV infection in newborns. Although recommendations for routine screening of newborns for CMV have been made by investigators and cost-efficient screening methods have been developed (Balcarek et al, 1993), few infants are actually screened. When hearing, vision, neurologic, and learning disabilities resulting from congenital CMV infection are enumerated, the magnitude of the problem and the size of the population affected seem to warrant basic CMV screening and identification, which would facilitate knowledgeable and timely audiologic, visual, educational, and medical service delivery for the children affected. Further, identification of congenital CMV infection would allow practitioners to not only use but also expand the existing knowledge base regarding multidisciplinary treatment and intervention for children with congenital CMV infection.

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