

Cochlear implant and thiamine-responsive megaloblastic anemia syndrome

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Thiamine-responsive megaloblastic anemia syndrome is a rare autosomal recessive disorder defined by the occurrence of megaloblastic anemia, diabetes mellitus, and bilateral sensorineural deafness, responding in varying degrees to thiamine treatment. We report a precedence case for the treatment of deafness associated with the typical triad of thiamine-responsive megaloblastic anemia in a 4-year-old boy who showed a poor use of preoperative hearing aids but demonstrated significant improvements in hearing ability 1 year after receiving a cochlear implant.

Thiamine-responsive megaloblastic anemia syndrome is a rare autosomal recessive condition, which was first described by Rogers et al.¹ The cardinal clinical manifestations of the syndrome are megaloblastic anemia, diabetes mellitus, and sensorineural deafness, all of which may respond in varying degrees to the administration of thiamine (vitamin B1) in pharmacological doses. Thiamine, also known as vitamin B1, is an essential dietary vitamin; the main sources are fresh fruits and vegetables. The active form of the vitamin (thiamine pyrophosphate) is a coenzyme required for several key steps in intermediary metabolism, including the oxidative decarboxylation of pyruvate and α -ketoglutarate.

Over the last 40 years, around 52 patients with the thiamine-responsive megaloblastic anemia syndrome have been described in the published studies. Mutations in the *SLC19A2* gene have been found in these thiamine-responsive megaloblastic anemia patients.² The defect results in a state of vitamin deficiency that causes metabolic aberrations in various tissues, including the auditory pathways. In general, hearing loss is irreversible, although some investigators have reported that thiamine therapy prevents further progression of deafness³ and more recently, Oishi et al,⁴ using an animal model, reported recovery of auditory function in 2 mice out of 3 after re-introducing thiamine.

Stagg et al⁵ postulated that the thiamine requirement for the cochlear or acoustic nerve cells is substantially higher than for other tissues, such that enteral thi-

amine may not prevent thiamine deficiency in cell types with high-energy usage at all times. This may lead to cell death in these most sensitive tissues. Particular neuron groupings, such as those in the brainstem, show an increased sensitivity to low thiamine levels, resulting in slow progressive and irreversible lesions.³ Moreover, auditory tests in some studies have pointed more toward brainstem sites of lesion.^{6,7} Indeed, a major concern before surgery is that a patient may have a proximal lesion in the brainstem, which may not be amenable to receiving a cochlear implant. No data were available to guide us regarding outcomes of cochlear implantation in patients with the thiamine-responsive megaloblastic anemia syndrome. This is the first report, to our knowledge, of cochlear implantation in thiamine-responsive megaloblastic anemia syndrome.

CASE

The male child was born at term by normal delivery after an uneventful pregnancy to distantly related Pakistani parents. He was the first-born child followed by a healthy sister and brother. No history of premature abortion, still birth, or offspring mortality was reported in his family. A genetic analysis to track inherited characteristics associated with thiamine-responsive megaloblastic anemia revealed that the parent's pedigrees met at their fourth generation on the grandmother's side, with no previous history of a similar disorder in any of the other family members. However, two of the child's cousins were profoundly deaf, but without

anemia or diabetes. According to the parents, the child was able to hear and speak a few words clearly up to age of two years but, thereafter, he stopped responding. At that time, he underwent audiologic evaluations that revealed bilateral profound hearing loss. Further blood workup showed hemoglobin of 3.2 g/dL (normal: 11.5-17.5) and a blood glucose level of 230 mg/dL (normal: 64.8-104.4). He underwent blood transfusion and was put on insulin. His megaloblastic anemia and diabetes recovered on thiamine, but no improvement in hearing was observed even after 2 years of treatment. He presented to our clinic at the age of 4 with little or no benefit from hearing aids.

In our hospital, an audiogram revealed profound sensorineural hearing loss in both ears. No reproducible evoked responses (ABR) were obtained even at 95 dB and no otoacoustic emission (OAE) responses were noted, bilaterally. Impedance tests showed normal ear canal volume and normal tympanograms. A computed tomographic scan of the temporal bones showed normal anatomy (**Figure 1**). The magnetic resonance imaging of the internal auditory canals and brain identified the presence of 8 nerves and no abnormality along the auditory pathways, bilaterally. He was assessed by our cochlear implant program committee and approved for cochlear implantation after extensive family counseling, exploring concerns and expectations.

RESULTS

The patient underwent straightforward a unilateral cochlear implant surgery with no complications. Following implantation, he showed progressive improvement in hearing as well as speech, validating our decision to proceed in this case. An implant-aided audiogram 1 year after operation revealed sound field responses in the region of 30 dB hearing level (**Figure 2**).

The auditory response to speech was assessed using the Listening Progress Profile (LIP)⁸ postoperatively at 6 and 12 months. The LIP provides a means of recording direct observations of different auditory skills (detection, discrimination, and identification) scored on a scale of 0 to 2 (never, sometimes, and always). The "always" responses are presented as a per cent score. Improvements were observed when results for 6 and 12 months were compared for sound detection (40% to 90%), discrimination between sounds (0%-93%), identification of environmental sounds (0%-50%), and identification of own name (0%-50%). According to subjective reports from the family, he always wore the implants, understood 70% of the usual conversation, and had marked behavior changes in the form of smiling, motivation, cooperation, and calmness.

DISCUSSION

Our patient had already had a long course of treatment without improvement in auditory function or language, even with the use of bilateral powerful hearing aids. We suggested cochlear implantation to the parents, who understood that the child may have underlying disorders of the auditory nerve, brainstem, or higher auditory pathways, and, therefore, the hearing may not improve after cochlear implantation. Our findings were, in fact, that he had marked improvement over time.

In this particular case, the profound loss may be more sensory in nature. For instance, Liberman et al⁷ reported normal cochlear function in an animal model



Figure 1. A computed tomographic scan of the temporal bones.

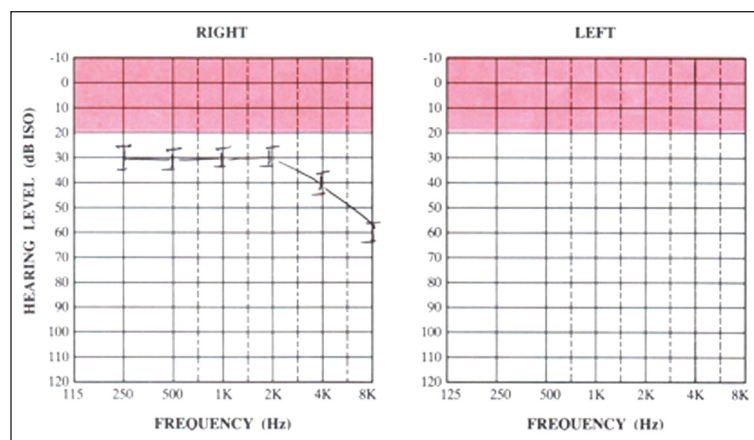


Figure 2. An implant-aided audiogram one year after operation.

of this syndrome when maintained on a high-thiamine diet. When challenged, however, with a low-thiamine diet, the ABR showed 40–60 dB threshold elevations, but only 10–20 dB elevation for OAE measures.^{4,7} Moreover, cochlear histological analysis showed a pattern uncommon for sensorineural hearing loss, which include: selective loss of inner hair cells after 1 to 2 weeks on low-thiamine diet and significantly greater inner than outer hair cell loss after longer low-thiamine challenges.⁷ In a study by Fleming et al,⁹ inner hair cells

expressed stronger affinity to the thiamine transporter than outer hair cells; interesting, apical inner hair cells showed more vulnerability to thiamine.

In conclusion, the exact cause of the hearing loss in this young patient with Thiamine-responsive megaloblastic anemia is still quite unclear, and there may be involvement at several levels. However, this case shows that substantial and important benefits can be obtained in bypassing the cochlear transduction mechanisms by cochlear implants.

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