Cochlear Implantation in Primrose Syndrome with a Novel ZBTB20 Gene Variant

Case Report

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Abstract

In this article, we aim to present details of the cochlear implantation procedure performed in a patient with Primrose syndrome, which is a rare genetic condition characterized by physical deformities, sensorineural hearing loss, and metabolic disorders. While its long-term prognosis is still under investigation, the absence of intraoperative and postoperative complications indicates promising findings. This designates cochlear implantation as a viable therapeutic approach for sensorineural hearing loss linked to Primrose syndrome. As cochlear implantation in cases with Primrose syndrome has not been discussed previously in the literature and our patient has recently been operated on, additional investigation is imperative to broaden the understanding of cochlear implant outcomes in this patient population.

Keywords: Hearing loss, genetic disease, Primrose syndrome, cochlear implantation, otorhinolaryngology, case report

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Introduction

Primrose syndrome (PS) is a rare genetic disease characterized by a range of distinctive features including macrocephaly, hypotonia, developmental and speech delay, behavioral disorders, ocular anomalies, sensorineural hearing loss, distal muscle wasting, and abnormal glucose metabolism. Facial phenotypes associated with PS include a high anterior hairline, sparse eyebrows, downslanted palpebral fissures, ptosis, high palate, torus palatinus, broad jaw, and large ears. Imaging techniques can detect various abnormalities such as Wormian bones, platybasia, outer ear calcification, cerebral calcification, agenesis or dysgenesis of the corpus callosum, and mild cerebral atrophy (1). PS was first described by David Primrose in a 32-year-old male patient with intellectual disability, muscle weakness in the lower limbs, calcified ear flaps, bone abnormalities, and torus palatinus (2).

The diagnosis of PS is established with characteristic features, and a heterozygous pathogenic variant in the *ZBTB20* gene is identified through molecular genetic testing (1). Hearing is commonly affected in PS. Calcification of the outer ear cartilage and enlarged auricles are also seen. Sensorineural hearing loss in

patients with PS is usually prelinguistic and can range from mild to moderate (1).

In this report, we present a case of PS with severe sensorineural hearing loss for which cochlear implantation (CI) was performed in our clinic. The lack of data on CI in patients with PS in the literature suggests that the hesitations we experienced in our case could guide future candidates.

Case Presentation

The patient was born at term via normal spontaneous vaginal delivery, with a birth weight of 3370 grams. At her sixth-month postnatal control, the baby was referred to the genetic clinic for macrocephaly and hypotonia. Physical examination revealed macrocephaly, frontal bossing, downslanted palpebral fissures, and strabismus (Figure 1a, b) Microarray analysis using Affymetrix CytoScan Optima array platform yielded normal results. Subsequently, whole exome sequencing was performed to investigate the underlying etiology, which revealed a heterozygous state for the c.1930A>C variant in the *ZBTB20* gene. Segregation analysis confirmed that the variant was a *de novo* variant (Figure 2). Based on the guidelines of the American College of Medical Genetics and Genomics, this variant was classified as likely pathogenic, considering both the development of amplified consensus genetic markers and segregation analysis results (3).

After PS was diagnosed and the metabolic and endocrinological problems (central hypothyroidism, blood sugar regulation problems) were stabilized, the patient presented to our audiology department with sensorineural hearing loss, a commonly seen component of PS. Otoscopic examination revealed normal external auditory canals and tympanic membranes bilaterally. Brainstem evoked response audiometry showed untraceable 5th peaks in both ears even at 90 dB. The tympanometry results were type-A in both ears. The patient was evaluated as a CI candidate. High-resolution computed tomography (CT) and magnetic resonance imaging of the temporal bones showed normal bilateral cochlear anatomy, auditory canals, and facial nerves. There was no evidence of external ear cartilage calcification, agenesis or dysgenesis in the corpus callosum. The patient used a hearing aid for six months, with no improvement reported by the family or observed clinically. Due to the lack of data in the literature on the CI results of patients with PS, a CI decision was made in the CI council together with pediatric psychiatry, metabolism, endocrinology, and child development specialists. Preoperative psychiatric evaluation revealed language and speech retardation, yet no intellectual disability. Since the patient had additional metabolic problems and there were no clear data on the CI results, CI was planned initially for the right-side, and the family was informed that the left side could be planned six months later, based on the results. As metabolic disorders negatively affect surgical outcomes, patient's thyroid medication usage, and preoperative and postoperative blood glucose levels were closely monitored. Throughout the patient's hospitalization, regular monitoring of fasting blood glucose levels revealed that they remained within the reference range.

We placed the CI in the right ear under endotracheal general anesthesia when the patient was two years old. The device (Nucleus® CI 422 from Cochlear Ltd.) was fully inserted through the round window without any intraoperative complications. Impedance, stapes reflex, and neural response telemetry were within the normal limits (Figure 3). The

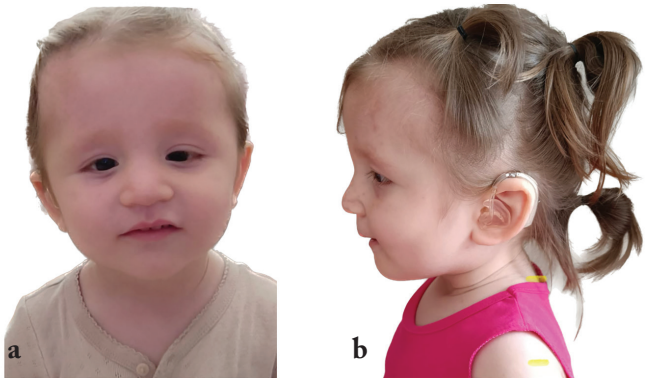

Figure 1. a, b. Clinical features of Primrose syndrome. Sparse body hair and eyebrows, macrocephaly, strabismus, high anterior hairline, downslanted palpebral fissures

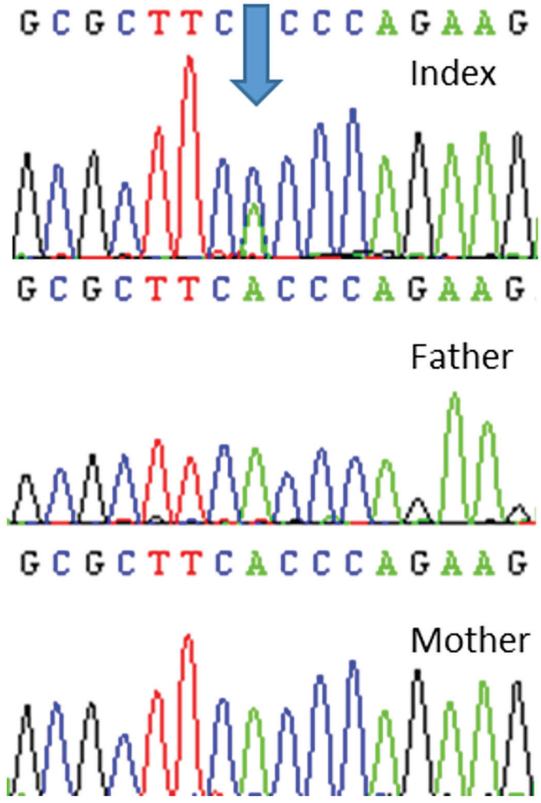

Figure 2. Sanger sequencing images of the family

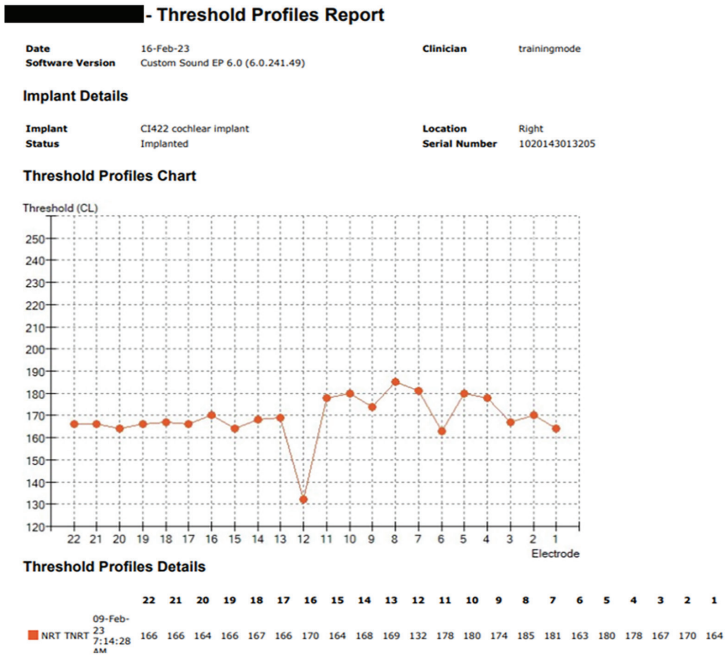

Figure 3. Intraoperative nerve monitoring showing the neural response telemetry responses in the right ear were within the normal limits

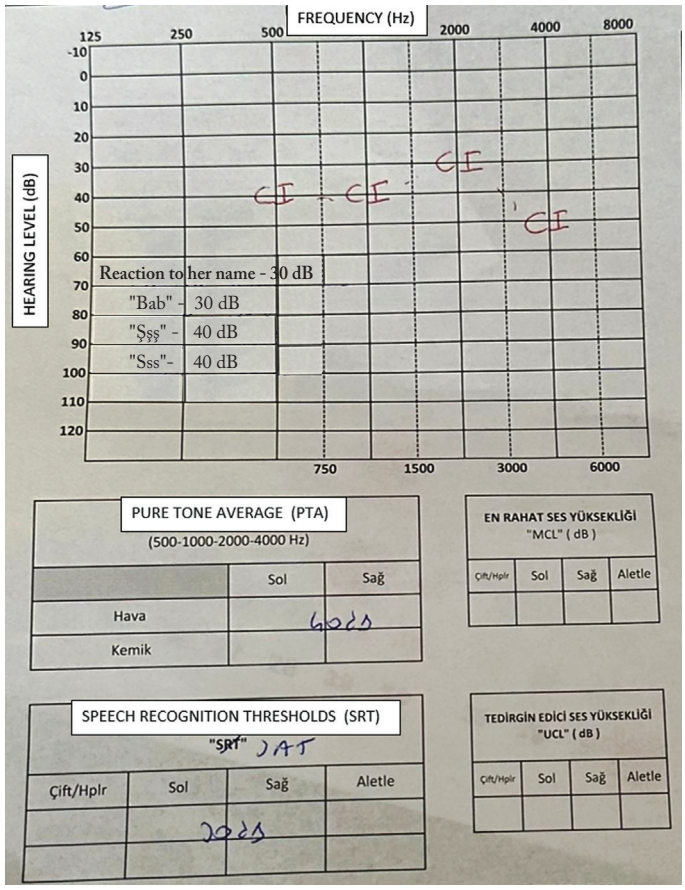

Figure 4. Postoperative third-month free field audiometry result

Stenvers and transorbital radiographs obtained postoperatively confirmed the appropriate location of the CI. The patient was discharged without any complications on the postoperative fourth day. Visual reinforcement audiometry in free field setup was performed in the postoperative third month, monosyllabic word recognition and response to name test revealed a pure tone average of 40 dB (Figure 4). The patient's family reported that she can form basic one-to-three-word sentences, and eagerly uses the implant device throughout the day, taking it off only when sleeping. The process of evaluating long-term CI hearing and speech results continues since it has been only three months since the operation. However, the fact that we have not encountered any problems intraoperatively or postoperatively encouraged us to present this case, for which the patient's parents' written and verbal informed consent have been received.

Discussion

Our patient had sensorineural hearing loss, and there was no calcification in the outer ear. To date, no study has specifically addressed the treatment of PS-related sensorineural hearing loss or CI.

Xie et al. (4) conducted a study investigating the effect of ZBTB20 on cochlear development and hearing in mice. Their findings suggest that the *ZBTB20* gene is crucial for the growth of the cochlear lateral non-sensory epithelium, hearing perception, and for overall cochlear development.

In a study by van Beeck Calkoen et al. (5), which included 423 children with sensorineural hearing loss, genetic mutations were identified as the most common underlying pathology, with 87 of all patients having a genetic disorder. Among these, only one patient was diagnosed with PS.

Arora et al. (1) provided a comprehensive description of the clinical characteristics, diagnosis, genetic disorders, and management of PS. Their study revealed that 12 of 13 adult patients and 21 of 27 pediatric patients with PS experienced hearing loss. In most cases, hearing loss was prelingual and predominantly sensorineural, with only one patient having a mixed-type hearing loss due to recurrent ear infections.

Carvalho and Speck-Martins (6) presented a case study in which a patient with PS had bilateral moderate mixed hearing loss. CT scans of the head revealed extensive and uniform calcification of both the pinnae and part of the external ear canals.

Posmyk et al. (7) described a case of PS involving bilateral partial hearing loss and calcified ears, as observed on CT scans. In another case report by Grímsdóttir et al. (8), a patient with PS displayed decreased hearing but no calcification was observed in the ears.

CI surgery has not previously been reported in these patients. In our case, CI was indicated due to bilateral sensorineural hearing loss, unsuccessful hearing aid trial for six months, and lack of improvement following conventional treatment. The

fact that our case has no long-term results is a shortcoming on its own. On the other hand, systemic metabolic problems of the patient should not cause the surgeon to consider delaying CI, since CI is crucial in supporting normal developmental milestones.

CI should be considered as a viable treatment option for sensorineural hearing loss associated with PS. While hearing aids can be used, early CI is essential for patients with bilateral hearing loss, enabling them to achieve developmental milestones and speech capabilities. Given the limited information available on CI outcomes in PS, we performed unilateral implantation and planned to consider contralateral implantation based on our results.

Informed Consent: Informed consent was obtained from the patient's legal guardians.

Authorship Contributions

Surgical and Medical Practices: B.A.T., A.G., C.B.A., E.A., İ.S., Z.M.Y., Concept: B.A.T., İ.S., Z.M.Y., Design: B.A.T., İ.S., Z.M.Y., Data Collection and/or Processing: B.A.T., A.G., C.B.A., E.A., İ.S., Z.M.Y., Analysis and/or Interpretation: B.A.T., A.G., C.B.A., E.A., İ.S., Z.M.Y., Literature Search: B.A.T., A.G., İ.S., Z.M.Y., Writing: B.A.T., A.G., C.B.A., E.A., İ.S., Z.M.Y.

Conflict of Interest: There is no conflict of interest to disclose.

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Main Points

- Sensorineural hearing loss and calcification of the outer ear cartilage are common in Primrose syndrome.
- Cochlear implantation should be planned quickly to prevent disruption of language and speech development after systemic and metabolic problems are checked in suitable syndromic children.
- Early implantation is important in both syndromic and normal children.
- While making the implant decision in syndromic children, physicians in other related branches should be included in the cochlear implant councils.

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