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Thiamine responsive megaloblastic Anemia and deafness: A rare case of Roger's syndrome with successful hearing rehabilitation by cochlear implantation

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ABSTRACT

Thiamine responsive megaloblastic anemia (TRMA), also known as Roger's syndrome, is an exceptionally rare autosomal recessive disorder stemming from mutations in the SLC19A2 gene responsible for encoding a thiamine carrier protein.

This syndrome manifests as the classic triad of megaloblastic anemia, sensorineural hearing loss, and diabetes mellitus. Here, we present the case of a one-and-a-half-year-old male infant born to non-consanguineous parents in India, a region where TRMA cases are seldom reported. At five months of age, the child exhibited the characteristic symptoms, prompting immediate treatment involving thiamine therapy, insulin administration, and blood transfusions. Notably, the child exhibited significant improvement in all aspects except for hearing loss, which conventional hearing aids failed to alleviate. However, following a cochlear implant procedure conducted within a few months, the child regained hearing abilities. This case underscores the importance of early recognition and intervention in the form of cochlear implant, demonstrating the potential to reverse TRMA symptoms and provide affected individuals with a substantially improved quality of life.

1. Introduction

Thiamine responsive megaloblastic anemia (TRMA) is a very rare autosomal recessive disorder with less than 80 cases being reported worldwide. It was first described by Porter, Roger et al., in 1969 [Porter, 1969]. Hence it is also known as Rogers' syndrome.

This disease is seen commonly in consanguineous marriages and in certain isolated communities [Oishi et al., 2002]. Some parts of the world have reported a few cases which includes Israel, Saudi Arabia and Lebanon. Specific groups/communities such as Alaskan kindred of native and ethnic Russian descent, and kindreds from Brazil, Japan, Oman, Tunisia, Italy (Venetian and other), Iran, India, and Pakistan, as well as Kashmiri families in Great Britain, ethnic Kurds, persons of northern European heritage, and African Americans too have developed the disease [Ortigoza et al., 2016; Zhang et al., 2021].

Rogers's syndrome is caused due to mutations in the gene SLC19A2 present on chromosome 1q23.2–23 that encodes for thiamine carrier protein h-THTRI which is a high affinity thiamine transporter present mainly in bone marrow, cochlear cells, and pancreatic beta cells. This transporter helps in uptake of thiamine by cells [Oishi et al., 2002]. Thiamine also known as vitamin B1 is required for various metabolic processes in our body and hence its defect can lead to the symptoms seen in this condition. Previously some studies have shown that thiamine is an essential component in hearing, and it is required in higher concentration by the cochlear and acoustic nerve cells. Hence its deficiency can lead to cochlear cell loss [Stagg et al., 1999].

Symptoms can manifest anytime between infancy to adulthood although commonly manifests in infancy. The typical triad of megaloblastic anemia, sensorineural hearing loss and diabetes mellitus constitutes this syndrome, though the sequence of appearance of symptoms may vary. Rarely other clinical features such as thrombocytopenia, short stature, optic atrophy, retinal changes, stroke and focal or generalized epilepsy, cardiovascular anomalies with sudden death, high-output heart failure, cardiac arrhythmia, and congenital heart defects such as atrial septal defect, are recorded [Spehar Uroic et al., 2020].

The diagnosis is based on clinical suspicion in patients presenting

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with the classical triad of symptoms. Early treatment with thiamine and control of diabetes has shown to be beneficial as per many studies. Although the hearing loss is not reversible once its set in, a cochlear implant can give the child future hearing as seen in a study by Hagr AA [Hagr AA 2014]. We present a 1.5-year-old male baby with Rogers' syndrome, a rare case being one among the few seen in India who underwent a successful cochlear implantation at our centre.

2. Case

Our patient, a 1.5-year-old Indian male baby was born to non-consanguineous parents as the first born in his family. The mother was a known diabetic and hypothyroid patient on treatment with both the states well under control during the antenatal period. The mother underwent an caesarean section due to post dated pregnancy. The birth weight of the child was 3.100 kg. Post partum period too was uneventful with no NICU stay.

Initially the baby had presented at 5 months of age with fever, vomiting, loose stools for 2 days and one episode of seizures which settled on medications. On physical examination he was severely lethargic with poor sensorium. There was tachycardia and tachypnoea. His weight was 6 kg and height 65 cm. Severe pallor and moderate degree of dehydration was noted. Other systemic examinations were normal.

On investigating further, the baby was found to be in Diabetic ketoacidosis and having severe anemia. Laboratory results showed haemoglobin- 3.1 gm%, MCV -96 fl, total count −15000 cells/mm^3 and random blood glucose – 589 mg/dl. Urine analysis revealed ketones 2+ and sugars 4+. Computed tomography (CT) brain was done in view of lethargic state and was found to be normal. Renal profile was normal.

The ketoacidosis and hyperglycaemic state were corrected immediately with intravenous fluids (normal saline) and insulin infusion at 0.1 U/kg/hour. One pint blood transfusion was given. The acidosis resolved gradually, and the patient improved. Loose stools and fever settled with symptomatic treatment. Blood culture and sensitivity showed growth of Spingomonus paucimobius and antibiotics were changed from ceftriaxone to ciprofloxacin as per the sensitivity report.

However, since there was a high suspicion of TRMA, thiamine therapy was started, and other work up initiated. A dose of 100 mg per day orally was started. An endocrinological evaluation revealed a normal thyroid profile. The diabetic state was brought under control. He has been under regular thiamine supplements since then and was kept on regular follow up.

Ophthalmological evaluation was normal. No other haematological abnormalities were detected.

A thorough otorhinolaryngological evaluation was done for this patient as the mother was apprehensive and doubtful that the baby was not responding to sounds. An initial behavioural observational audiometry (BERA) test revealed the possibility of profound hearing loss. Otoacoustic emissions were absent bilaterally. Tympanogram revealed type A curve with bilateral absent reflexes. The diagnosis of sensorineural hearing loss was confirmed by BERA. As there was no improvement in hearing despite starting thiamine, hearing aid was fitted to the patient. In view of no improvement with hearing aids, a cochlear implant was planned.

Meanwhile, based on the provisional diagnosis genetic evaluation was attempted and mutations for SLC19A2 gene were found. Hence the diagnosis of TRMA was confirmed.

3. Results

High Resolution Computed Tomography (HRCT) of the temporal bones and MRI temporal bones revealed no abnormalities. As part of pre op work up, ECHO was done and found to be normal. An ultrasound of the abdomen showed multiple reactive abdominal lymph nodes. The patient was given antibiotic therapy for the same from the paediatricians. Pneumococcal and meningococcal vaccinations were given 6 weeks prior to surgery. Counselling to the parents and the prognosis and risks of surgery were explained to the parents. At 1.5 years of age, the baby underwent a right sided cochlear implant.

A peculiar intraoperative finding noted was the occurrence of a linear fracture at the implant site while the application of non traumatic soft tissue retractor with mild depression of the bone (see Fig. 1). The well for the receiver stimulator was designed such that the fracture line gets incorporated in it to avoid the formation of extradural hematoma (see Fig. 2).

No postoperative complications were noted. In view of the intraoperative occurrence of fracture, the child's vitamin D and calcium levels were evaluated and were noted to be insufficient. Switch on of the implant as well as mapping was done after 10 days, which was uneventful followed by which the patient has been receiving rigorous speech therapy. At present, the child shows good response to sounds and improvements in hearing and speech. Hence, a cochlear implant seems to be a reasonable option to restore hearing in TRMA patients. In our case a clear improvement in hearing and speech was seen post cochlear implantation.

4. Discussion

TRMA, an autosomal recessive ailment rooted in mutations within the SLC19A2 gene, typically manifests with a triad of symptoms: megaloblastic anemia, sensorineural hearing loss, and diabetes mellitus [Spehar Uroic et al., 2020]. Prompt thiamine treatment proves efficacious in managing the condition.

Upon initial presentation, our patient exhibited a hemoglobin level of 3.1 gm%. Subsequent commencement of thiamine therapy resulted in an impressive increase to 10 gm% over a span of 34 days, with continuous daily dosages of 100 mg orally. Studies in the literature corroborate this swift amelioration of hemoglobin levels within a month of thiamine initiation. A study by Akin L et al. demonstrated a rise in Hb from 6.6 gm % to 10.6 gm% within just 16 days of thiamine supplementation [Akın et al., 2011].

Research by Alzahrani et al. posits that high-dose thiamine therapy progressively reduces the need for insulin, ensuring better control over anemia and hyperglycemia [Alzahrani et al., 2006]. This is also established in our case. Our patient had initially presented in diabetic ketoacidosis and after recovery, the patient was kept on insulin. Due to the initiation of thiamine for TRMA, the blood sugar levels were also

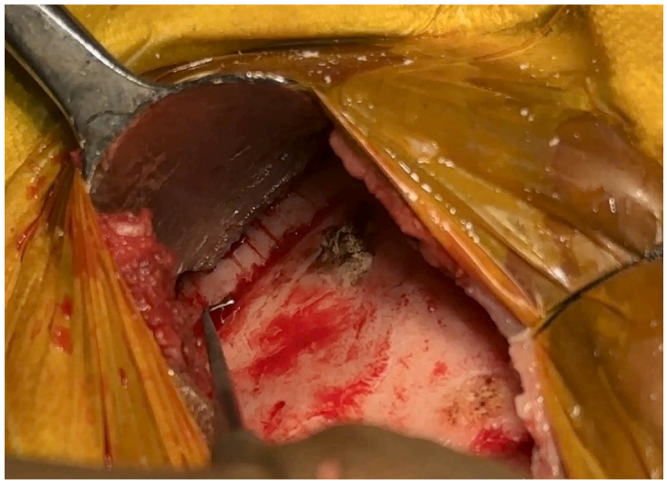

Fig. 1. Occurrence of temporal bone fracture during the application of non-traumatic retractor during the right sided cochlear implant surgery. This was a noteworthy finding during the surgery when exposure for the implant well was done.

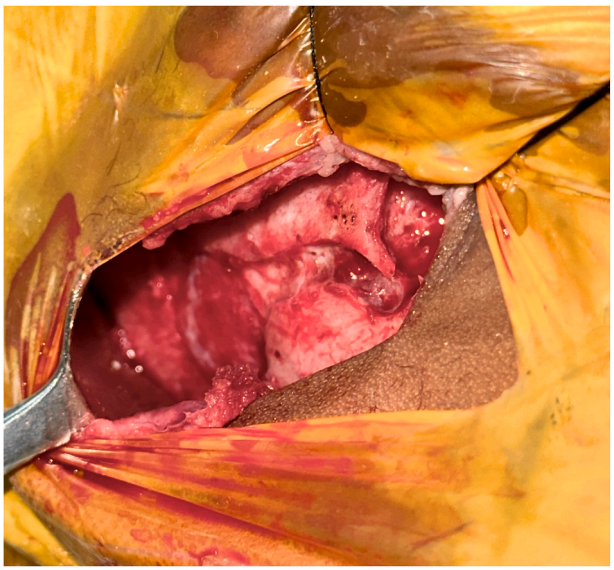

Fig. 2. The well for the implant was drilled so as to incorporate the temporal bone fracture line and prevent the formation of extradural hematoma.

stabilised over the period of time and insulin supplementation eventually stopped.

Sensorineural hearing loss, a hallmark of TRMA, may or may not co-occur with the other symptoms initially and often worsens over time. While the precise cause remains elusive, animal models suggest selective inner hair cell loss in TRMA contributes to this progressive hearing impairment. Disruption of the SLC19A2 gene and variations in thiamine diet in mouse models have been linked to cochlear function loss Liberman et al., 2006; Pinkus et al., 2001; Fleming et al., 2003.

A study by Akin L et al. revealed moderate sensorineural hearing loss in a child despite thiamine initiation at 4 months; screening initially showed normal results but later detected the hearing loss at 20 months of age [Akın et al., 2011]. In our study, hearing loss was detected around the age of 1 year. Early identification of congenital hearing loss through Neonatal screening programs using Otoacoustic emission tests can be instrumental in spotting such abnormalities sooner.

Past studies have shown that hearing aids yield no improvement in these patients, making cochlear implants a viable alternative. A 4-year-old Pakistani patient, as reported by Hagr AA, saw significant hearing and language improvement within a year of undergoing cochlear implantation while on thiamine therapy [Hagr AA 2014].

Low vitamin D levels have been associated with bone demineralisation and increased risk of fractures [Herdea et al., 2023]. This was also established in our case who had significantly low vitamin D levels that were a cause of fracture of the skull bone at the region of placement of the receiver stimulator of the implant. In India, vitamin D deficiency is rampant as it affects more than half of the paediatric population [Venkatesh et al., 2021]. The use of Vitamin D and calcium supplements during the preoperative preparation period of children should be speculated so as to avoid the complications encountered in our case.

Noteworthy technique used in our case was drilling of a well for the receiver stimulator at the site of fracture. This also acted as a means of decompressing the site and preventing hematoma formation.

In conclusion, any infant displaying the three cardinal symptoms should be assessed for TRMA. Early thiamine therapy may not prevent hearing loss but can enhance the patient's anemic and diabetic condition, making it crucial for suspected cases. Genetic analysis is essential for diagnosis confirmation. Regular follow-ups and adjustable thiamine therapy are necessary. While all aspects of the disease can be managed conservatively, hearing loss can be addressed with cochlear implants, offering hope and improved hearing. Therefore, a combination of cochlear implants and thiamine therapy can afford TRMA patients a normal life with good hearing.

Author's contribution

Dr Hetal Marfatia: Conception and design of the study and guided the authors to work for the publication. Final approval of the version to be published.

Dr Anoushka Sahai: Responsible for collection, compiling and analysis of all data. Drafting the article and revising it critically for important intellectual content.

Dr Kartik Narkhede: Drafting the article. Helping data collection and analysis.

Dr Monankita Sharma: Data collection and compilation of data.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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