CASE REPORT

THIAMINE-RESPONSIVE MEGALOBLASTIC ANAEMIA WITH HYPOTHYROIDISM, A PUZZLING ASSOCIATION

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Background: Thiamine-responsive megaloblastic anaemia (TRMA) is characterized by the classic trio of diabetes mellitus, sensorineural hearing loss, and megaloblastic anaemia, typically emerging subtly between infancy and adolescence. Administration of high-dose thiamine often yields improvements in anaemia and occasionally in diabetes. Uncommon manifestations include optic atrophy, congenital heart defects, short stature, and stroke. In this specific case, a 5-year-old diagnosed with insulin-dependent diabetes mellitus (IDDM) since the age of one presented with symptoms such as polyuria, fever, and vomiting, revealing an HbA1c of 10.64. Further examinations disclosed compromised hearing and vision. A negative antibody workup and a thyroid profile indicating hypothyroidism prompted additional investigations, including Brainstem Evoked Response Audiometry (BERA) and retinal examination, confirming bilateral sensorineural hearing loss and maculopathy, respectively. A comprehensive blood count unveiled megaloblastic anaemia. Genetic profiling confirmed a homozygous mutation in the SLC19A2 gene, thus diagnosing TRMA. An early diagnosis, coupled with genetic confirmation, enables timely intervention, with patients responding positively to high-dose thiamine. Genetic counselling plays a pivotal role in enlightening families about the disease and its inheritance patterns, fostering awareness and understanding.

Keywords: TRMA; Hypothyroid; Diabetes mellitus; Hearing loss; Optic nerve

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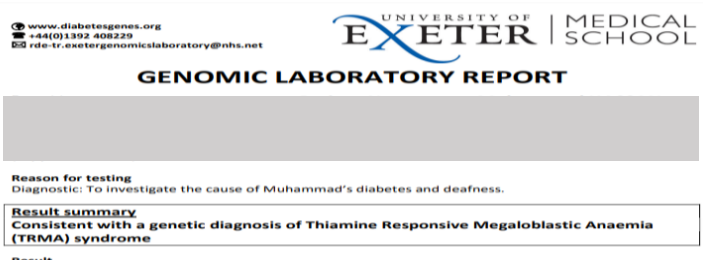
INTRODUCTION

Thiamine-responsive megaloblastic anaemia (TRMA) is a rare autosomal recessive condition caused by a mutation in the SLC19A2 gene and is classically characterized by the triad of diabetes mellitus, sensorineural hearing loss and megaloblastic anaemia.[1] It usually presents between infancy and adolescence but the cardinal findings are not present initially. The anaemia, and sometimes the diabetes improves with high doses of thiamine.[2] Apart from classic characteristics, less common presentations include optic atrophy, congenital heart defects, short stature and stroke[3]. Our case shows a rare association and the first case from Pakistan is genetically proven and no association in the literature of hypothyroidism with TRMA is found. Thiamine-responsive megaloblastic anaemia with hypothyroidism, a puzzling association

CASE REPORT

We present the case of a 5-year-old child with a known case of IDDM for 1 year of age presented with complaints of polyuria, fever and vomiting. His HBA1c turned out to be 10.64 confirming his diabetes. On doing further examination, we learned that the patient has diminished hearing and vision and also required one PCV transfusion in the past. Autoantibodies workup for type 1 DM was negative and the thyroid profile showed hypothyroidism with TSH >100 uIU/ml and FT4 0.5 nm/l. For diminished hearing and vision, we sent the patient for BERA and retinal examination which revealed bilateral sensorineural hearing loss and maculopathy respectively. Keeping TRMA in view we looked at the patient's complete blood count which revealed megaloblastic anaemia. Furthermore, we sent the patient's genetic profile showing a homozygous mutation in the SLC19A2 gene confirming Thiamine responsive megaloblastic anaemia (TRMA) as shown in the following figure: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GENOMIC LABORATORY REPORT

Reason for testing
Diagnostic: To investigate the cause of Muhammad's diabetes and deafness.

Result summary
Consistent with a genetic diagnosis of Thiamine Responsive Megaloblastic Anaemia (TRMA) syndrome

We kept the patient on Thiamine supplements along with Insulin adjustment and the patient responded well requiring no more transfusions and the requirement of insulin was decreased gradually.

DISCUSSION

Thiamine-responsive megaloblastic anaemia (TRMA) is a rare autosomal recessive condition caused by a mutation in the SLC19A2 gene encoding the high-affinity thiamine transporter 1 and is classically characterized by the triad of diabetes mellitus, sensorineural hearing loss and megaloblastic anaemia.[4] An affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.[5]

In our presented case, the initial diagnostic journey involved comprehensive blood profiling, assessment of vitamin B12/folic acid levels, and HbA1c testing. The patient's diminished hearing and vision prompted further investigations, including BERA testing to confirm sensor neural hearing loss and retinal examination for maculopathy. It's worth noting that TRMA can also be associated with optic atrophy and stroke, which would necessitate MRI confirmation. Ultimately, genetic analysis revealing a homozygous SLC19A2 gene mutation provided the conclusive diagnosis of Thiamine responsive megaloblastic anaemia (TRMA).

Thiamine supplementation remains a cornerstone in managing TRMA. While it effectively addresses anaemia, its impact on diabetes management is more nuanced. Thiamine can delay the onset of diabetes to some extent, but its efficacy varies among individuals. Unfortunately, sensorineural hearing loss, a significant aspect of TRMA, remains unresponsive to thiamine treatment.

Our case emphasizes the challenges inherent in diagnosing rare genetic conditions like TRMA. The multifaceted clinical presentation necessitates a comprehensive approach, including genetic analysis, to ensure accurate identification. Early diagnosis holds paramount importance, as it enables timely intervention and potentially better outcomes, particularly in terms of anaemia management. Genetic counselling plays an essential role in informing families about the nature of the condition, its inheritance patterns, and potential implications for future generations.

The onset of megaloblastic anaemia is between infancy and adolescence and can be treated with thiamine but can result in a relapse with treatment withdrawal as red cells remain microcytic. It is also associated with irreversible sensorineural hearing loss not responsive to thiamine treatment. The third and foremost presenting symptom of triad diabetes mellitus is non-type 1 in nature and can occur anytime between infancy and adolescence. Furthermore, diabetes is partially responsive to thiamine and can only delay its onset in some individuals.[6]

The initial investigation includes a complete blood picture along with vitamin b12/ folic acid levels and HBA1c. Sensorineural hearing loss can be confirmed with BERA. The other symptoms such as stroke and optic atrophy can be further confirmed by an MRI and retinal exam respectively. The diagnosis is further confirmed by genetic analysis which will reveal a homozygous mutation in the SLC19A2 gene. Treatment with oral thiamine will result in improvement of anaemia and can delay the onset of diabetes in some individuals however, sensorineural hearing loss will be irreversible.

Learning Points:

1. Consider Rare Disorders

This case emphasizes the importance of considering rare disorders, even in cases with atypical presentations. Thiamine-responsive megaloblastic anaemia (TRMA) is exceptionally rare, and its coexistence with hypothyroidism is even rarer. Healthcare professionals should maintain a broad differential diagnosis and be vigilant for unusual associations.

2. Diagnostic Challenges

Rare disorders like TRMA are often initially misdiagnosed due to their rarity and lack of awareness among healthcare providers. Early diagnosis can be challenging but is crucial for timely intervention. Collaborative efforts among specialists may be necessary for accurate diagnosis.

3. Genetic Testing

Genetic testing is a valuable tool in confirming the diagnosis of rare genetic disorders. In this case, genetic testing identified mutations in the SLC19A2 gene, confirming TRMA. Genetic insights not only validate the condition but also provide a basis for understanding the underlying genetic mechanisms.

4. Multidisciplinary Approach

Complex medical cases like this one often require a multidisciplinary approach. Collaboration among haematologists, endocrinologists, geneticists, and other specialists is essential to provide comprehensive care, accurate diagnosis, and appropriate management for patients with rare and complex conditions.

5. Timely Intervention

Timely intervention can significantly impact patient outcomes. In this case, thiamine supplementation and levothyroxine replacement therapy led to a rapid improvement in the patient's symptoms and blood counts. Early recognition and prompt treatment are crucial for managing rare disorders effectively.

6. Raising Awareness

Raising awareness about rare disorders among healthcare professionals is essential to reduce diagnostic delays. Educational initiatives and continued medical training can help increase knowledge about rare conditions, facilitating earlier diagnosis and treatment.

In summary, this case report underscores the importance of vigilance, collaboration, and genetic testing in diagnosing and managing rare disorders like TRMA, especially when they present with unexpected comorbidities. Learning from such cases contributes to the broader understanding of rare diseases and can ultimately improve patient care and outcomes.

CONCLUSION

Thiamine-responsive megaloblastic anaemia (TRMA) is a rare condition which is confirmed by a genetic mutation in our patient. The paediatricians should be vigilant with patients having diabetes to look for other features leading towards this disease. Timely diagnosis along with genetic confirmation will help in treating the patient early as exogenous thiamine has a good response in these patients. Genetic counselling should also be done so that the families are aware of this disease and its inheritance patterns.

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