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Transcobalamin Deficiency with the Mutation of Tcn2 in Children with the Primary Diagnosis of Methylmalonic Academia

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Abstract

Transcobalamin deficiency as a rare autosomal recessive disorder and methylmalonic acidemia is an autosomal recessive disorder of amino acid metabolism. Based on the common presentation of methylmalonic academia and Transcobalamin deficiency, in this case report, we presented rare cases of Transcobalamin deficiency in children with the primary diagnosis of methylmalonic academia. As the genetic test indicated the definite diagnosis, we fortunately treated our patient based on the genetic result to solve B12 deficiency and it showed promising outcomes.

Key Words: Child, Mutation, Transcobalamin deficiency.

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1- INTRODUCTION

Cobalamin ((vitamin B12) is a water-soluble vitamin with a crucial role in the functioning of various enzymes (1). In blood, it is attached to haptocorrin (HC) and to transcobalamin (TC) which advocates endocytosis of cobalamin (2). After eating, cobalamin binds to intrinsic elements and enters the enterocytes. In circulation, it is complexed with transcobalamin and taken into the cells by the transcobalamin receptor. The receptor is encoded by CD320 on the short arm of chromosome-19 (3).

TC deficiency is a rare autosomal recessive disorder with methylmalonic acidemia and homocystinuria (2). Within the first months of life, the clinical characteristics of TC deficiency are failure to thrive, diarrhea, and anemia. Anemia is typically megaloblastic and sometimes occurs with pancytopenia or isolated erythroid hypoplasia. It has been misdiagnosed as leukemia (4).

Besides, methylmalonic acidemia is an autosomal recessive disorder of amino acid metabolism, involving a defect in the conversion of methylmalonyl-coenzyme A (CoA) to succinyl-CoA. Patients usually present at the age of 1 month to 1 year with neurologic expressions, such as seizure, encephalopathy, and stroke (5).

Based on the common presentation of methylmalonic academia and TC deficiency, in this case report, we aimed to present a rare case of TC deficiency in children with the primary diagnosis of methylmalonic academia.

2- CASE PRESENTATION

In this case report, we presented three children of first-cousin consanguineous parents (**Table 1, Fig. 1** and **2**). They all had similar symptoms and TC deficiency was confirmed by the genetic assessment. We presented a rare TC deficiency in a 7-year-old boy referred to the clinic of Akbar hospital, Mashhad, Iran. In his past medical history in infancy, he was suspected of methylmalonic acidemia due to metabolic symptoms. However, in the neonatal screening, metabolic disorders were checked and were unremarkable. In his second admission in 2 years, his laboratory results showed normal HCT (34.5), SGOT (20.5), SGPT (9.4), and Ammonia (80.0). Moreover, he had a low level of RBC (33.37) and Hb (10.7). Furthermore, he had high lactate (27.0) and PLT (613). Venous blood gas was also measured and showed the following results: PH: 7.39, PCO2: 33.0, PCO2: 61.0, HCO3: 20.3, and BE: -3.2.

Regarding the high level of methylmalonic in the laboratory results and the inheritance of methylmalonic academia, first, methylmalonic academia was diagnosed for him and he was treated accordingly. When he was referred to our clinic, we requested genetic testing for the monogenic disorder to have a definite diagnosis.

Furthermore, at 7 years of age, he and his parents underwent a molecular genetic assessment for TC deficiency. Their DNA was extracted with the standard method and they found that all of them had one likely pathogenic homozygote mutation. They found that the mutations of TCN2 led to TC-II deficiency which is an autosomal recessive disorder. Therefore, he was treated with cobalamin.

A second case dedicated to a 6-month-old girl with developmental delay and movement disorder. She also could not stand steadily. She referred to the pediatric endocrinologist with the same symptoms and underwent a genetic analysis. In her early genetic assessment, mutated homozygosity of TCN2 NM-000355.4c.940+1G>A was found and it was recognized to be likely pathogenic in the ACMG classification. Due to this result, Transcobalamin II deficiency (275350) with an autosomal recessive

inheritance was diagnosed. Notably, she was the cousin of the first case and her early diagnosis helped clinicians to diagnose the disease in the first case.

The third case belonged to a 3.5-year-old boy with microgonasia, bone-marrow hypoplasia, abnormal gait, developmental delay, nail problems, and macular dystrophy who was referred for genetic assessment by the pediatric rheumatologist. In the whole exome sequencing, a homozygote likely pathogenic variant was identified in the TCN2 gene, and eventually, Transcobalamin II deficiency was confirmed.

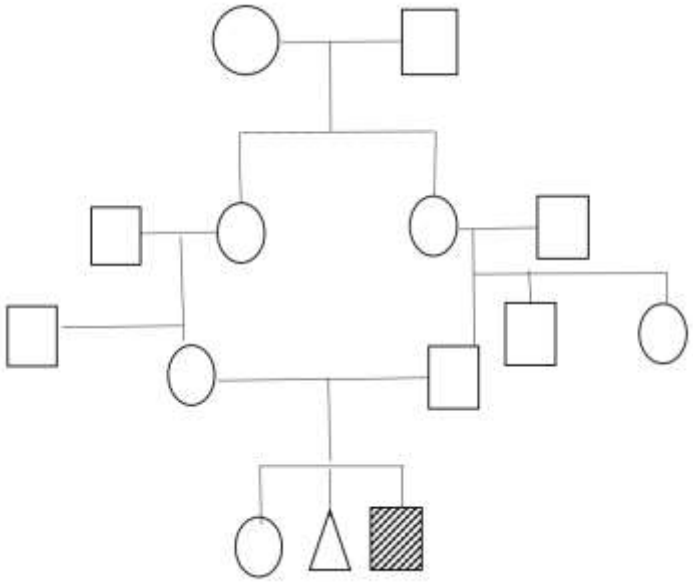

Fig. 1: The pedigree of case 1

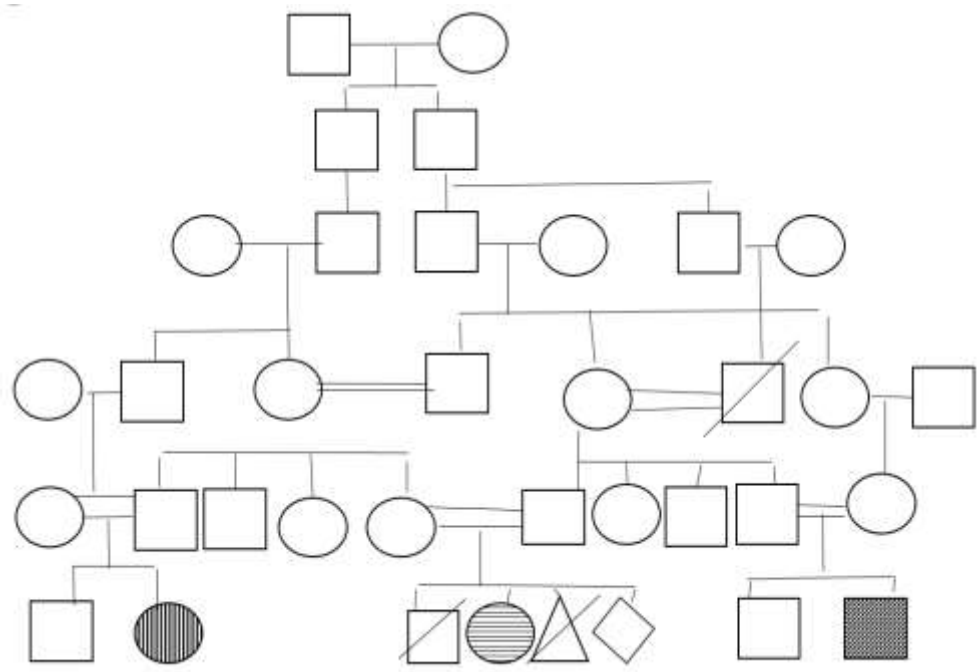

Fig. 2: The pedigree of case 2

Table-1: The genetic results of the patients

Case		Zygosity	Gene: variant	Acmg classification	Associated disease (omim phenotype)	Inheritance
Case 1	Child	Homozygous	Nm_000355.4 C.940+1g>a	Likely pathogenic	Transcobalamin ii deficiency	Autosomal recessive
Case 2	Child	Mutated homozygous	Tcn2 nm_000355.4 c.940+1g>a	Likely pathogenic	Transcobalamin ii deficiency (275350)	Autosomal recessive
	Mother	Heterozygous				
	Father	Heterozygous				
Case 3	Child	Homozygote	Tcn2: (613441) nm_000355.4 c.1211dup p.leu405fs	Likely pathogenic	Transcobalamin ii deficiency (275350)	Autosomal recessive
		Homozygote	Fmn2 (606373) nm_020066.5 c.162_163del p.gly55fs	Vus	Intellectual developmental disorder, autosomal recessive 47 (616193)	Autosomal recessive

3- DISCUSSION

Cobalamin is absorbed at the terminal ileum through the endocytosis that is mediated by an enterocyte membrane receptor. Consequently, it secrets in the bloodstream where it binds to the vector protein haptocorrin, formerly known as transcobalamin I. In the enterocyte, the compound of intrinsic factor plus cobalamin gets separated and cobalamin reaches the portal circulation where it is bound to transcobalamin (named as transcobalamin II (TC)) (6).

TC deficiency is a rare autosomal recessive disorder. Deletions or insertions in the TCN2 gene are its most common mutation. It can be diagnosed by clinical features and laboratory results (7). Most of the genes that could elucidate variations in vitamin B12 concentrations are stated from Caucasian population (8).

So far, 60 cases of TC deficiency and 25 pathogenic mutations in TCN2 gene have been reported (9). This condition presents diverse symptoms such as neurological and psychiatric features or classic megaloblastic anemia. Even gastrointestinal problems can occur in these patients (10). As these patients have increased homocysteine and methylmalonic acid in combination or methylmalonic aciduria alone (11), we reported a rare case of TC deficiency with a primary diagnosis and treatment of methyl malonic academia.

It also may mimic neonatal leukemia or severe combined immunodeficiency disease (10). Therefore, a differential diagnosis is mandatory to reach a promising outcome. It is undoubtedly important to diagnose it as soon as possible because delayed diagnosis and consequent treatment may induce irreversible neurological defects (2) and can be life-threatening (10). As it was mentioned, the second child's early diagnosis helped clinicians with the management of her cousin as our first case.

Despite intensive searching, we did not reach a guideline on the treatment of TC deficiency concerning the form of B12 supplement, the dosage and the duration of administration, the route of administration,

and follow-up. A previous study reporting on 30 patients, noted that administering 1 mg of hydroxocobalamin or cyanocobalamin weekly for a lifetime can be the most appropriate prescription (10) that was the same as what we prescribed.

4- CONCLUSION

As previously discussed, the genetic testing indicated a definite diagnosis. We, fortunately, treated our patients based on the genetic result to solve B12 deficiency and it showed a promising outcome. Our report emphasized the importance of timely diagnosis of TC deficiency and prompt commencement of treatment for disease control.

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