

DIAGNOSIS OF CLASSICAL HOMOCYSTINURIA IN A PEDIATRIC PATIENT WITH COMPLEX PHENOTYPE: CASE REPORT AND MULTIDISCIPLINARY APPROACH

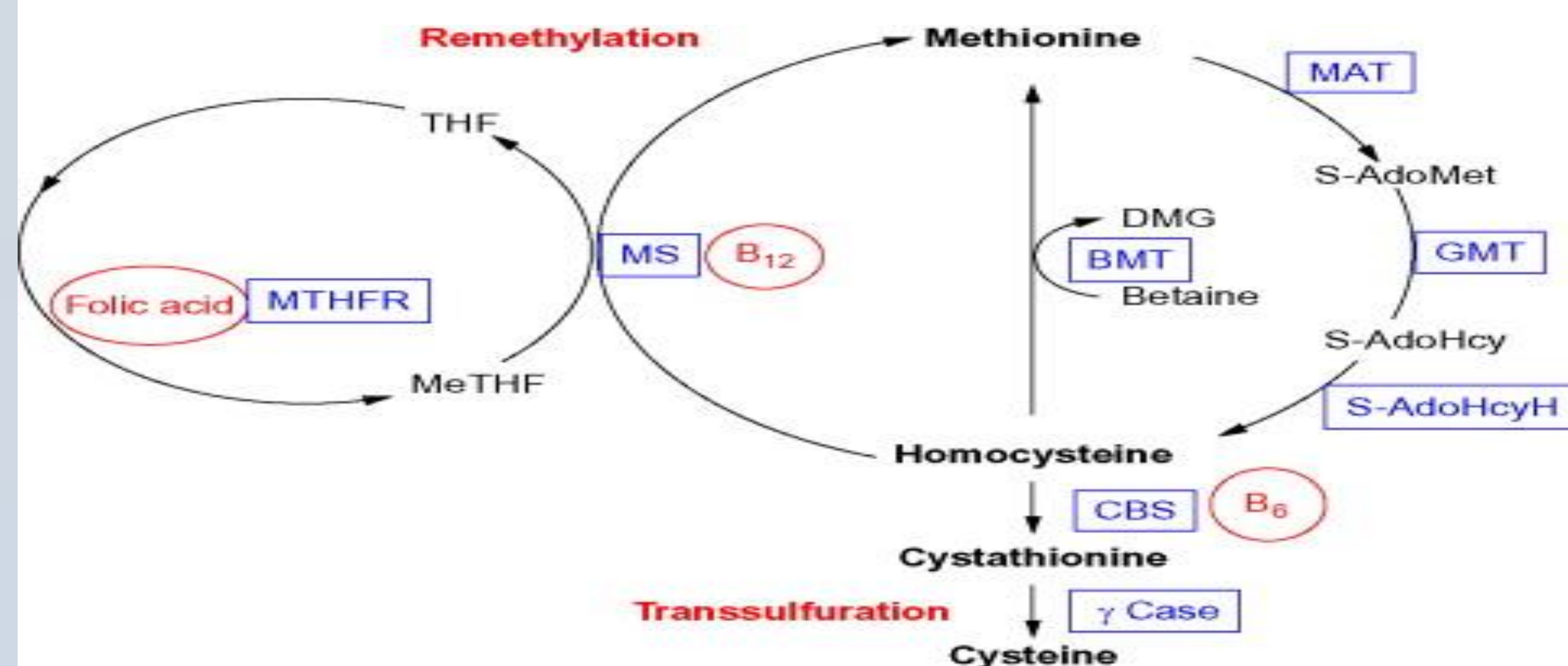
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BACKGROUND

Classical homocystinuria is an autosomal recessive disorder of sulfur amino acid metabolism caused by cystathionine beta-synthase (CBS) deficiency, leading to systemic accumulation of homocysteine and methionine. The clinical phenotype is highly variable and includes neurodevelopmental delay, skeletal dysmorphisms, ocular complications, and cardiovascular involvement. Early diagnosis is crucial to prevent severe neurological and vascular outcomes.



METHODS

We report the case of a 7-year-old boy of Tunisian origin, admitted to our department for suspected rickets. Clinical history revealed psychomotor delay, speech difficulties, unsteady gait, and skeletal deformities. Family history showed parental consanguinity. The patient underwent multidisciplinary clinical evaluation with biochemical tests, imaging (X-ray, MRI, ECG, echocardiogram), and genetic testing (NGS clinical exome sequencing). Plasma homocysteine and methionine were measured by a High-Performance-Liquid Chromatography HPLC.

RESULTS

On admission, physical examination revealed dysmorphic features (pectus carinatum, hallux valgus, clinodactyly, enlarged wrists), muscle hypotrophy, and speech delay. Serum homocysteine and methionine levels were markedly elevated (229.16 $\mu\text{mol/L}$ and 225 $\mu\text{mol/L}$, respectively). Genetic analysis identified biallelic mutations in the CBS gene, confirming the diagnosis of classical homocystinuria. Treatment was started with pyridoxine (70 mg/day), folic acid (10 mg/day), hydroxocobalamin (1 mg/day), later supplemented with betaine (Cystadane). A low-protein, methionine-restricted diet was also introduced. Follow-up showed good therapeutic compliance, progressive reduction of homocysteine levels, and overall clinical improvement.

Gene	Inheritance model	SNV	(GRCh38/hg38), exon	Allele frequency GnomAD v4.1	HGMD
CBS	AR	NM_000071.3: c969G>A p.(Trp323Ter);homozygous	Chr21:43062381 C>T (exon 11 di 17)	Absent	Present (CM123371)

CONCLUSIONS

This case highlights the importance of an early and comprehensive diagnostic workup in pediatric patients with multisystemic phenotype and suggestive family history. The multidisciplinary approach enabled timely diagnosis of classical homocystinuria and initiation of targeted therapy, improving long-term prognosis. Consanguinity and migration background represent risk factors that warrant attention in the evaluation of complex pediatric cases.

