D'Ambrosio MF, et al., J Genet Genomic Sci 2023, 8: 045
DOI: 10.24966/GGS-2485/100045

HSOA Journal of Genetics & Genomic Sciences

Case Report

Two Rare Mutations in Cases of Late-Onset cblC type

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Abstract

Background: Combined Methylmalonic Aciduria (MMA) and homocystinuria are a genetically heterogeneous disorder of cobalamin metabolism, caused by homozygous or compound heterozygous mutation in the MMACHC gene on chromosome 1p34. Clinical manifestations and the age of onset of clinical signs and symptoms are variable. May be associated with this condition, which involves hyperhomocysteinemia, cases of epilepsy, seizures and neurological disorders. For these conditions is essential early diagnosis and appropriate treatment as early as possible.

Case Report: We report two different cases: of a 41-years-old man, with an apparently unexplained elevated plasma level of homocysteine and no neurologic symptoms, and of a 35-years-old woman with a history of epilepsy who consults for high level of homocysteine. Both diagnosed with combined methylmalonic acidemia and homocystinuria cblC variant. We found in both the patients a condition of compound heterozygosity for 2 mutations: a mutation in exon 4, c .440 G> C p.Gly147Ala, and an insertion of a base in exon 2, c.271dupA (p.Arg91LysfsX14).

Conclusion: These cases suggest that even if combined methylmalonic aciduria with homocystinuria is a rare entity, its identification is essential so as to allow the initiation of an effective early treatment to avoid the pathophysiological progression and the serious clinical consequences of this disease, even in cases of late-onset cblC.

Keywords: Homocisteine; Metabolic disorder; Neurological disorder

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Citation: D'Ambrosio MF, D'Apolito M, Leccese A, D'Andrea G, Cordisco G, et al. (2023) Two Rare Mutations in Cases of Late-Onset cblC type. J Genet Genomic Sci 8: 045.

Received: October 27, 2023; **Accepted:** November 06, 2023; **Published:** November 13, 2023

Background

Combined Methylmalonic Aciduria (MMA) and homocystinuria is a genetically heterogeneous disorder of cobalamin (cbl; vitamin B12) metabolism. As a result of this enzyme deficiency, methylcobalamin and adenosylcobalamin are not synthesised: the former plays a central role as a cofactor for methionine synthase, the latter is a cofactor for the mitochondrial enzyme methylmalonyl-CoA mutase, which is involved in the breakdown of methylmalonic acid [1]. Different forms of the disease have been classified according to the complementation groups of the cells in vitro: cblC, cblD, cblF and cblJ. The cblC variant is more common and more severe. The mutations for methylmalonic aciduria and homocystinuria, cblC type, have been identified in a region of the short arm of chromosome 1 containing the MMACHC gene (MMACHC gene, OMIM*609831). This is an autosomal recessive disorder, so a homozygous or compound heterozygous mutation in this gene causes the disease [2]. An incidence of cblC ranging from of 1:100,000 to 1:200,000 births has been estimated, with a higher frequency in the Hispanic population (about 1:37,000) [3]. Clinical manifestations and the age of onset of clinical signs and symptoms are variable. Most of described patients show the severe, early-onset disease [1,4].

Affected individuals may present with developmental, haematological, neurological, metabolic, ophthalmological, and dermatological clinical findings. Although considered a disease of infancy or childhood, some individuals develop symptoms in adulthood [5]. Rarely, affected individuals present with gait ataxia and cognitive decline in adulthood. Treatment with hydroxocobalamin can improve the clinical features of early-onset disease and prevent clinical late-onset disease. In the absence of neurological disease, clinical suspicion and diagnosis may be delayed or missed [6,7]. Correct diagnosis and effective treatment are essential.

Recent cases raise the possibility that derangements of cobalamin metabolism could be a contributing factor in cases of hemiconvulsion-hemiplegia-epilepsy, as well as febrile seizures in general [8].

We report two different case: of a 41-years-old man, with an apparently unexplained elevated plasma level of homocysteine and no neurologic symptoms, and of a 35-years-old woman with a history of epilepsy who consults for high level of homocysteine. Both diagnosed with combined methylmalonic acidemia and homocystinuria cblC variant.

Cases Presentations

We present two clinical cases. One is a 41-year-old male patient from Southern Italy with a history of suspected homocystinuria deficiency. The patient initially showed no signs or symptoms. Plasma homocysteine was measured following an occasional analysis. The analysis showed elevated plasma homocysteine levels tHcy: 113 µmol / L (range: 5-12 µmol / L). Other relevant values found in the haematological analysis were: folate: <40 nmol / L (range: 3.1–17.5 nmol / L) and serum vitamin B12 levels: 748 pmol / L (range: 191–663 pmol /L). However, after treatment with folic acid, which lasted 10

months, and benexol (a drug belonging to the therapeutic category of vitamin-based Vitamin B1 + B6 + B12) lasted three months, showed no significant reduction in plasma levels of homocysteine, with a high value of 96 µmol / L. Subsequently, the dosage of the metabolites on sample extract from the patient's serum was also performed, through the technology of tandem mass spectrometry (QTrap instrument in MRM mode) resulting in the following values: L-Methionine 36.87 ± 2.77 µmol / L (range: 11 ± 35), L-Phenylalanine 7.96 ± 1.52 µmol / L, Ratio L-Methionine / L-Phenylalanine 4.6 (range: 0.26 ± 0.56).

The second case came to our attention in October 2020, a 35-year-old woman from southern Italy with a personal history of minor episodes of sporadic epilepsy diagnosed in treatment and under follow-up for Neurology, as well as, after blood tests, high homocysteine levels equal to 53 µmol / L (range: 5-12) without reaching a clear etiology of the same. After three months due to therapy with hydroxocobalamin, serum homocysteine levels decreased to 16,28 µmol / L.

For both a defect in homocysteine metabolism with genetic etiology has been hypothesized.

Methods

Patients DNA was extracted from a blood sample and using an automated method for MagCore® HF16 Plus. Later, the open-reading frame and flanking exon sequences of CBS and MMACHC genes were sequenced after gene amplification with standard protocol of PCR. PCR products were purified with Plates MultiScreen PCRµ96 (Millipore). Then, products were analyzed on an ABI 3130xl DNA Sequencer (Applied Biosystems). Sequencing files were processed using Sequence Analysis software (Applied Biosystems) and were assembled and analyzed using Sequencer 4.7 Software.

The analysis of the CBS gene (Cystathionine beta-synthase) was carried out but no mutation was found. Then the complete screening of the MMACHC gene (cobalamin C associated metabolism gene) was performed [9]. We found in both the patients a condition of compound heterozygosity for 2 mutations: a mutation in exon 4, c .440 G> C p.Gly147Ala, and an insertion of a base in exon 2, c.271dupA (p.Arg91LysfsX14). These mutations have already been described in the literature and associated with Combined Methylmalonic Aciduria (MMA) and homocystinuria condition [2].

Results and Discussion

CblC disease is a multisystem disease, including metabolic instability, pancreatitis, renal failure, intellectual impairment, optic nerve atrophy, spinal cord, and basal ganglia injury. Depending on the age of disease onset, cblC disease patients are divided into early-onset type and late-onset type. The late-onset cblC defect is a rare disease and unfortunately, diagnosis is often delayed. Raising awareness for this disorder can significantly improve patients' outcome and perspective by timely initiation of targeted treatment. Late-onset cblC disease was first reported in the 1980s [10].

Cases so far described in literature were characterized by cognitive and psychiatric problems. In the case of the two patients here described the diagnosis of the disease was overlooked due to absence of signs in the first case and of the rarity of this disease in general. The problem of epilepsy in the second patient was never associated with this pathology in the past.

The age of onset in the two patients was 41 years and 35 years. Total plasma Hcy concentrations in the patients were markedly increasing, which is a useful indicator for the prompt diagnosis of cblC disease, although the identification of high homocysteine values in both cases was occasional. Following suspicion of cblC deficiency in patients, the main genes involved, CBS and MMACHC, were studied. Both the patients have a condition of compound heterozygosity for two mutations in the MMACHC gene: a mutation in exon 4, c .440 G> C, p.Gly147Ala, and an insertion of a base in exon 2, c.271dupA, p.Arg91LysfsX14.

Therefore, late-onset cblC disease cannot be considered a homogeneous clinical entity. The wide clinical heterogeneity of cblC disease likely depends on the nature of the different MMACHC mutations. When juvenile/adult patients with hyperhomocysteine in plasma present with neurological symptoms that are not consistent with common neurological diseases, cblC disease needs to be considered. The organic acid screening and genetic analysis for MMACHC gene mutations should be implemented to allow for early diagnosis and to improve prognosis.

Although its occurrence is rare, late-onset combined methylmalonic aciduria and homocystinuria, cblC type, should be considered in making a differential diagnosis in patients who present with neurological symptoms that are not consistent with common neurological diseases, especially when cognition, the pyramidal tract and peripheral nerves are involved.

The therapy based on vitamin b12 undertaken promptly led to excellent results in both cases studied. In case 1 the plasma homocysteine levels tHcy were 113 µmol / L before therapy. Thanks to the therapy with Vitamin B12 - Neocytamen 1000 in intramuscular vials for 4 weeks and then an oral vial every two days, in less than a month the plasma homocysteine value has dropped from 113 µmol / L to 39 µmol / L. The plasma homocysteine value, although remaining higher than the range of normal values, underwent a significant decrease in a short time.

In case 2, although out of the normal range, serum homocysteine levels dropped from 53 µmol / L to 16.28 µmol / L after three months with hydroxocobalamin therapy. Homocysteine remains slightly higher than the norm but has decreased considerably, demonstrating that even in cases of late-onset cblC, diagnosis and timely therapy are important for the welfare and health of the patient.

Conclusion

In this study, we analyzed the clinical presentations and treatment outcomes of late-onset cblC in two patients. Most patients reported with cblC deficiency show severe clinical manifestations at an early age [4]. The late-onset cblC deficiency is rare and difficult to diagnose due to its wide spectrum of clinical manifestations. Up to now, no more than 100 late-onset cblC cases have been reported [7,11].

When juvenile or adult patients present only with high serum level of homocysteine or with also neurological symptoms that are unexplained by common neurological diseases, cblC deficiency needs to be considered. The organic acid screening and genetic analysis for MMACHC gene are recommended to the early diagnosis.

These cases suggest that even if combined methylmalonic aciduria with homocystinuria is a rare entity, the correct diagnosis is important to avoid the pathophysiological progression and the serious clinical

consequences of this disease, because early treatments usually can bring clinical improvements, even in cases of late-onset cblC.

References

1. Weisfeld-Adams JD, Morrissey MA, Kirmse BM, Salveson BR, Wasserstein MP, et al. (2010) Newborn screening and early biochemical follow-up in combined methylmalonic aciduria and homocystinuria, cblC type, and utility of methionine as a secondary screening analyte. Mol Genet Metab 99: 116-123.

2. Lerner-Ellis JP, Tirone JC, Pawelek PD, Doré C, Atkinson JL, et al. (2006) Identification of the gene responsible for methylmalonic aciduria and homocystinuria, cblC type. Nat Genet 38: 93-100.

3. Rosenblatt DS, Aspler AL, Shevell MI, Pletcher BA, Fenton WA, et al. (1997) Clinical heterogeneity and prognosis in combined methylmalonic aciduria and homocystinuria (cblC). J Inherit Metab Dis 20: 528-538.

4. Fischer S, Huemer M, Baumgartner M, Deodato F, Ballhausen D, et al. (2014) Clinical presentation and outcome in a series of 88 patients with the cblC defect. J Inherit Metab Dis 37: 831-840.

5. Bodamer OA, Rosenblatt DS, Appel SH, Beaudet AL (2001) Adult-onset combined methylmalonic aciduria and homocystinuria (cblC). Neurology 56: 1113.

6. Roze E, Gervais D, Demeret S, Baulny HO, Zittoun J, et al. (2003) Neuropsychiatric disturbances in presumed late-onset cobalamin C disease. Arch Neurol 60: 1457-1462.

7. Huemer M, Scholl-Bürgi S, Hadaya K, Kern I, Beer R, et al. (2014) Three new cases of late-onset cblC defect and review of the literature illustrating when to consider inborn errors of metabolism beyond infancy. Orphanet J Rare Dis 9: 161.

8. Myers KA, Dudley RW, Srour M (2018) Hemiconvulsion-Hemiplegia-Epilepsy in a girl with cobalamin C deficiency. Epileptic Disord 20: 545-550.

9. Grandone E, Martinelli P, Villani M, Vecchione G, Fischetti L, et al. (2019) Prospective evaluation of pregnancy outcome in an Italian woman with late-onset combined homocystinuria and methylmalonic aciduria. BMC Pregnancy Childbirth 19: 318.

10. Shinnar S, Singer HS (1984) Cobalamin C mutation (methylmalonic aciduria and homocystinuria) in adolescence. A treatable cause of dementia and myelopathy. N Engl J Med 311: 451-454.

11. Liu Y, Wang Q, Li X, Ding Y, Song J, et al. (2015) First Chinese case of successful pregnancy with combined methylmalonic aciduria and homocystinuria, cblC type. Brain Dev 37: 286-291.

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