Expanding the spectrum of 3MC syndrome: A case series illustrating clinical variability, genetic heterogeneity, and diagnostic challenges in the genomic era

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INTRODUCTION

3MC syndrome is a rare autosomal recessive disorder of development, characterized by distinctive craniofacial gestalt and multisystem anomalies. It results from biallelic mutations in genes of the lectin complement pathway, namely MASP1, COLEC11 and COLEC10, which disrupt the non-canonical function of this pathway in guiding neural crest cell migration during embryogenesis. This report is to detail the profound clinical and genetic heterogeneity of 3MC syndrome through a series of three cases, highlighting the spectrum of disease expression and the practical challenges of molecular diagnosis in the genomic era.

CASE REPORT

We present three patients evaluated in a reference center for rare diseases. Notably, all patients, despite some variability, shared recognizable phenotypic characteristics, particularly a similar facial gestalt. Prior to molecular testing, facial photographs of each patient were analyzed using the Face2Gene application and in all three instances, the platform´s algorithm reported 3MC syndrome as a primary differential diagnosis with a high degree of confidence. Case 1 is a 22-year-old female from a consanguineous union with a classic phenotype including laryngotracheomalacia, unilateral hearing loss, and diastasis recti, with a confirmed homozygous pathogenic variant in the MASP1. Case 2 is a 14-year-old boy of non-consanguineous parents with cleft palate, bilateral conductive hearing loss, radioulnar synostosis, learning disabilities and epilepsy. Despite the high diagnostic suspicion, molecular confirmation is still pending due to the identification of two homozygous variants of uncertain significance (VUS), in MASP1. Case 3 is a 3-year-old female of non-consanguineous parents with a severe phenotype characterized by complex congenital heart disease, crossed renal ectopia, associated with mild neurodevelopmental delay and distinct dysmorphological characteristics. Two compound heterozygous VUS were found in COLEC11.

IMAGE – FACIAL PHENOTYPIC CHARACTERISTICS OF PACIENTES 1, 2 AND 3

DISCUSSION AND CLOSING COMMENTS

These cases illustrates the vast phenotypic variability of 3MC syndrome, from classic presentations to those with severe, life-threatening visceral malformations, underscoring that prognosis is often dictated by systemic involvement rather than the facial phenotype alone. The cases endorse genotypic heterogeneity and highlight the diagnostic impasse of VUS. We emphasize that a robust clinical diagnosis should guide immediate management, while family-based segregation studies are pursued as the gold standard for resolving molecular uncertainty and enabling accurate genetic counseling. This case series expands the documented spectrum of 3MC syndrome and provides a practical framework for the integrated clinical-genomic approach required for diagnosis and management. It underscores that deep phenotyping combined with systematic familial genetic investigation is essential for navigating the complexities of rare disorders.

REFERENCES

1. Ashton CJ, Perveen R, Beaman G, Crisponi G, González-Del Angel A, Garza-Mayén G, Alcántara-Ortigoza MA, O'Sullivan J, Clayton-Smith J. 3MC syndrome: molecular findings in previously reported and milder patients expand the natural history and phenotypic spectrum. Clin Dysmorphol. 2023 Jan 1;32(1):7-13. doi: 10.1097/MCD.0000000000000443. Epub 2022 Nov 28. PMID: 36503917.
2. Rooryck C, Diaz-Font A, Osborn DP, Chabchoub E, Hernandez-Hernandez V, Shamseldin H, Kenny J, Waters A, Jenkins D, Kaissi AA, Leal GF, Dallapiccola B, Carnevale F, Bitner-Glindzicz M, Lees M, Hennekam R, Stanier P, Burns AJ, Peeters H, Alkuraya FS, Beales PL. Mutations in lectin complement pathway genes COLEC11 and MASP1 cause 3MC syndrome. Nat Genet. 2011 Mar;43(3):197-203. doi: 10.1038/ng.757. Epub 2011 Jan 23. PMID: 21258343; PMCID: PMC3045628.
3. Gajek G, Świerzko AS, Cedzyński M. Association of Polymorphisms of MASP1/3, COLEC10, and COLEC11 Genes with 3MC Syndrome. Int J Mol Sci. 2020 Jul 31;21(15):5483. doi: 10.3390/ijms21155483. PMID: 32751929; PMCID: PMC7432537.