A DOUBLE HIT GENETIC DISORDER IN A CASE OF PROGRESSIVE WEAKNESS AND HYPERMOBILITY

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INTRODUCTION. The use of next-generation sequencing (NGS) in clinical practice is increasingly accessible and has changed the molecular approach to presumably hereditary diseases. However, the massive information obtained from these tests are still not fully manageable. The poor phenotypic individualization of the analysis can make the diagnosis unfeasible and, in some cases, produce spurious results. One of the pitfalls in this process is the clinical conditions determined by two pathogenic variants, complex situations known as double hit genetic disorders.

CASE REPORT A male patient, 14 years old, son of consanguineous parents, presented at the age of 2 with difficulty walking. The condition progressed slowly, symmetrically and with a distal predilection, in a length-dependent rhythm. While walking, the patient presented marked hyperextension of the knee, denoting marked joint hypermobility accompanied by hyperelasticity of the skin.

PROPAEDEUTICS EMG revealed normal conduction and diffuse denervation with a distal predilection, characterizing a distal motor neuropathy. His WES revealed a class 4 homozygous variant in the IGHMBP2 gene (c.2796delC, p.Cys932TrpfsTer46) related to hereditary distal motor neuropathy (dHMN) type VI and CMT2S . As this gene did not explain hypermobility, a new WES search, using a virtual panel for hypermobility genes was conducted and revealed a class 4 homozygous variant in the ALDH18A1 gene (c.121 C>T, p.Arg41Cys), related to cutis laxa.

CONCLUSIONS If all patients had different symptoms caused by a single gene, the propaedeutic process would boil down to artificial intelligence. However, in several situations, the composition of symptoms may have more than one explanation, as attested by Hickam's saying (“A man can have as many diseases as he damn well pleases”). This case underscores the importance of a detailed neurological examination, which, associated with comprehensive complementary assessment, has been described under the term “deep phenotyping”.