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Editorial

Old and new syndromes

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From the womb to the adult
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Doctors treat patients, not statistical averages.
A patient needs a doctor, not a committee.
John P. Peters

Keywords

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What is a genetic syndrome? For a long time this definition was reserved to those patients with a set of features recurrent together, in which a genetic origin was certain or highly presuntive. Dysmorphic features, Multiple Congenital Anomalies and Mental Retardations (MCA/MR) were main clinical elements in most of the patients. The authors of the first description frequently gave the eponimic name to these syndromes.

The application of new molecular and cytogenetics technologies, such as FISH and array-CGH, has amplified in the last two decades the opportunity to identify new genetic conditions in patients with a clinical spectrum MCA/MR. Microdeletions and microduplications syndromes, telomeric rearrangements defects, genomic imprinting abnormalities, uniparental disomies, are some examples of the so called "new genetic" syndromes. This process is still active and in some patients with complex phenotypes, multiple molecular defects may be identified to explain the genotype-phenotype relationship. It is the case of patient we recently observed and described with a paternal uniparental disomy of chromosome 14, associated to a microdeletion and abnormalities of the genomic imprinting [1]. Some well known syndromes as the Wiedemann-Beckwith, Cornelia-de Lange and Prader-Willi were reclassified in the more recent years, on the basis of the molecular mechanisms responsible for the phenotype in each patient.

In the past, when such process of etiopathogenetic relationship failed, the term of association were often used to term MCA/MR conditions. In this case, an acronym derived by the initial letters of the main features often revealed an useful definition. VATER/VACTERL, CHARGE, MURCS, DIDMOAD, LEOPARD, CATCH22, are some of such famous acronyms in clinical genetics. Sometimes, the discovery of a genomic or epigenetic defect in one or some patients with one of these conditions, allowed its nosological alignment. It is the case, for example, of the CHARGE syndrome, due to a defect of a gene mapped on the long arm of 8 chromosome, for a long time considered an association due to environmental factors or having a multifactorial inheritance.

In addition, in some MCA/MR patients, the identification of a molecular defect in one of the steps of a metabolic pathway, within one or more cellular lines, allowed to include these syndromes among the inherited metabolic diseases [2]. The Smith-Lemli-Opitz syndrome is the classical example of such conditions, due to a defect of 7dehydrocholesterol-Reductase, showing high blood levels of 7dehydrocholesterol and low cholesterol levels. Multiple congenital defects of such syndrome are related to this metabolic defect and consequent lack of precursor of hormones, biliary acids and salt, neurotransmitters, receptors.

The use of molecular genetic tests allowed to change the nosology of some monogenic syndromes. We now know, for example, that achondroplasia, Muenke syndrome, thanatophoric dysplasia, hypochondroplasia depend on different mutations of the same gene, the *FGFR3*. In the same way, a single mutation of one gene may be responsible for different phenotypes also within the same family, on the basis of different and specific epigenetic interactions. Both Noonan and LEOPARD syndromes are typical examples of such effect inducing different phenotypes.

In conclusion, genetic syndromes are a complex and heterogeneous family of conditions whose main features are MCA/MR. At once, in most of cases its diagnosis were only clinical. Nowadays, in a progressively increasing number of patients and cases, we may define their cytogenetic as well as molecular defect, also useful to address both genetic counselling and follow-up.

Declaration of interest

The Author declares that there is no conflict of interest.

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