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Lesson 10

In-depth rare diseases

RAREDUCANDO DIGITAL EDUCATION

Variable common immunodeficiency

What is it?

Variable common immunodeficiency is a disease characterised by malfunctioning of the immune system and in particular the response to foreign agents by antibodies. The pathology is associated with a more or less profound alteration of the ability to produce antibodies by B lymphocytes resulting in high susceptibility to different types of infections (mainly pneumonia, meningitis, skin or bowel infections), certain types of tumours (particularly lymphomas) and the development of systemic and organo-specific autoimmune diseases. It usually occurs after the age of two and in any case during childhood or adolescence.

Common variable immunodeficiency (CVID) is the most frequent congenital immunodeficiency. This pathology is characterised by reduced levels of antibodies, resulting in lower immune defences, increased susceptibility to infections and a tendency to develop autoimmune diseases and malignancies. The heterogeneity of clinical manifestations has so far prevented clarification of the genetic basis of the disease. Recent data have shown that under the term CVID several diseases are actually grouped not only on the cells responsible for the production of antibodies, but also on other cells involved in the immune response, including T lymphocytes. The development of rational strategies to combat CVID therefore requires two tools: 1) a classification system allowing patients to be grouped according to the cellular type with a functional defect; 2) an in-depth knowledge of the defect in cells presenting dysfunction. Our project fits into this perspective. We have identified a group of CVID patients with T lymphocyte failure and demonstrated that the common defect is the reduction of cell levels of Vav, a protein that regulates the plasticity of the cytoskeleton and essential for the activation of T lymphocyte, on which the subsequent production of antibodies by plasma cells depends. The aim of the project is to identify the genetic cause of the reduced production of this molecule in T lymphocyte. The current protocol of therapy in CVID patients involves the administration of antibodies at frequent intervals, which not only has a negative impact on the quality of life of these patients, but often results in serious complications of anaphylactic type. Identifying the defective gene may provide these patients with viable therapeutic alternatives, both pharmacological and gene.

How is variable common immunodeficiency transmitted?

Most cases are sporadic, not hereditary. However, it is believed that around 20 % may be familiar (more than one affected person is found in the same family), autosomal dominant transmission (80 percent) or recessive autosomal transmission (20 percent). In dominant autosomal forms, one parent with the mutation has one in two chances of transmitting it to each of his or her children; not all subjects with mutation, however, become ill (incomplete penetrance). In autosomal

recessive forms, parents are healthy carriers of the mutation, while each child of the couple has a 4 chance of being ill. A mutation of the TACI gene is present in approximately 10 per cent of cases; deficits have been identified in other genes involved in the immune response of B and T lymphocytes (BAFFR, ICOS, CD19, CD81, CD20, CD21) and TNF receptors (NFRSF13B and TNFRSF13C).

How does the diagnosis of variable common immunodeficiency occur?
The diagnosis starts with a clinical evaluation and is confirmed by laboratory tests that measure the levels and function of the antibodies. If there are appropriate indications from family history, genetic analysis can also be carried out, with mutations being investigated in TAC1 or ICOS genes. In couples pregnancies where the genetic defect has already been identified in one or both parents, it is possible to make a prenatal diagnosis.

What are the treatment possibilities currently available for variable common immunodeficiency?
The therapeutic interventions cover three aspects in particular: periodic administration of antibodies (replacement therapy), to try to prevent infections, antibiotic therapy to deal with ongoing infections and, in patients with autoimmune disorders, adequate immunosuppression therapy. Periodic monitoring should be carried out to detect as early as possible possible cancer forms.

Reference centers for variable common immunodeficiency

https://www.orpha.net/consor/cgi-bin/Clinics_Search_Simple.php?lng=IT&LnkId=3469&Typ=Pat&CnsGen=n&fdp=y&from=rightMenu

Useful links:

https://www.malattierare.eu/pages/rivista/Immunodeficienza-comune-variabile-idA80

https://www.osservatoriomalattierare.it/malattie-rare/immunodeficienze/8151-immunodeficienza—common-variable-the-prof-carlo-agostini-explain-what-things

https://www.ospedalebambinogesu.it/immunodeficienza-comune-variabile-cvid--80140/

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