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MANAGEMENT OF GENETIC DISEASES: PRESENT AND FUTURE

TRATAMIENTO DE LAS ENFERMEDADES GENÉTICAS: PRESENTE Y FUTURO

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ABSTRACT

Today, the number of genetic diseases is around 10000 conditions, affecting to 6%-8% of all populations. This review shows us how the discovery of genetic variants in our genome, this facilitated to know with precision about the mechanisms physiopathological, and hence to recognize those target points susceptible to modifications, through therapeutical strategies different with palliative proposals, increase life expectancy, or improve qualities of life. These therapies are diverse, using drugs for polygenic diseases, nutritional therapy, special formulas, enzyme replacement therapies, hematopoietic stem cell transplant, substrate reduction, oligonucleotides, and gene therapy. These genetic diseases are heterogeneous clinically with a very low frequency; nevertheless, open to the possibility of research in new strategies for more genetic disease, that today, furthermore, are orphans.

Key words: Genetic diseases; Genetic Therapy; Hematopoietic Stem Cells; Transplant; Therapy (source: MeSH NLM).

RESUMEN

El número de enfermedades genéticas se estima que podrían ser más de 10 000 condiciones diferentes, afectando alrededor del 6-8% de la población. La presente revisión nos muestra la importancia del descubrimiento de las variantes patogénicas en nuestro genoma que nos permite conocer con mayor precisión cuales son los mecanismos fisiopatológicos y, por lo tanto, conocer puntos dianas susceptibles de modificaciones mediante diferentes estrategias terapéuticas para poder palear los síntomas y signos, aumentar la expectativa de vida, mejorando así la calidad de vida de los pacientes que tienen algunas de estas enfermedades genéticas. Las diferentes terapias que existen en la actualidad son muy diversas como fármacos de uso en patologías comunes, terapia nutricional, fórmulas especiales, terapias de reemplazo enzimático, trasplante de órganos y células hematopoyéticas, reducción de sustrato, oligonucleótidos y la terapia génica. Al ser las enfermedades genéticas clínicamente heterogéneas, abre la posibilidad de poder investigar cada vez más nuevas estrategias en un mayor número de enfermedades que en la actualidad están olvidadas.

Palabras clave: Enfermedades genética; Terapia genética; Células Madre hematopoyéticas; Trasplantes; Terapias (fuente: DeCS BIREME).

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INTRODUCTION

A rare disease is defined by the appearance frequency. That is why, for example, in Europe it is referred as the one with an incidence of less than 1/2000 people. The number of patients who are affected is estimated between 6% to 8% of the general population. In our country there are no studies that define the real number of affected people, therefore it is estimated that they are approximately 2 million of Peruvian people[1]. Nonetheless, some studies that were done estimate that the percentage of affected people by a rare disease may be between 3.5% to 5.9%.

The etiology of rare disease has a genetic origin in 80% of the total cases, and the other 20% has an unknown origin. The genetic origin can be divided into three groups: i) the ones that are produced by variants in a unique nucleotide (SNV, nucleotide variant), ii) variants of multiple nucleotides (MNV, multinucleotide variant) and iii) variants in the number of copies (CNV, copy number variation). The first two variants mainly produce monogenic diseases, which are estimated by the World Health Organization (WHO) to number more than 10,000 entities[1]. Pathogenic (or probably pathogenic) CNVs that cause microdeletion/microduplication syndromes; where the most frequent have a prevalence between 1/1 000 to 1/25 000[3]; although, it has been reported that in fetuses the incidence of CNVs is higher reaching 0.7%[4]. It is important to clarify that not all genetic diseases are rare. (e.g. Down syndrome, Klinefelter syndrome)[5]. Of this large group of conditions, about 500 diseases have a targeted treatment[6].

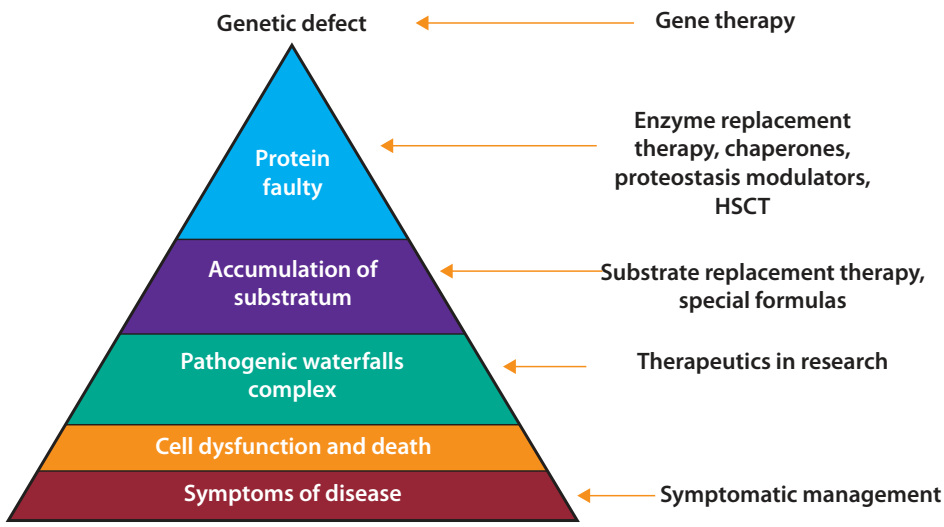
It should be noted that genetic diseases account for up to 71% of pediatric hospitalizations[7] and cause between 20% and 30% of deaths in this age group[8]. This proportion of patients generates a large economic impact on health systems; thus, an Australian study carried out in a population-based cohort in 2010 found that patients with rare diseases generated 10.5% of hospital expenses[9], in addition to a longer hospital stay than their peers without genetic conditions[7].

The clinical manifestations of genetic diseases are very diverse, i.e. they have a great clinical or phenotypic variability and can manifest as hypotonia, delayed psychomotor development, intellectual disability, epilepsy, neuroregression, congenital anomalies, short stature, microcephaly, primary immunodeficiencies, schizophrenia, autism spectrum disorders, conduct disorders, attention deficit hyperactivity disorder, dementia, abnormal movements and cancer. There are even entities, such as infantile cerebral palsy, in which a genetic component was not previously described and it is now considered that up to 20% of cases have a genetic cause[1]. It is important to point out that genetic diseases can appear at any stage of life, from prenatal to adulthood[10].

Since the end of the 20th century, thanks to the decoding of DNA and a better understanding of the pathophysiology of genetic diseases, targeted therapies, namely those that are directed at the factor or factors that initiate the disease, have been progressively and steadily increasing, which is aided by bioinformatics[11].

Therapies for genetic diseases are available and their use has been approved by international institutions such as the Food and Drug Administration (FDA[12,13] and the European Medicine Agency (EMA)[14,15]. On the other hand, there is a great expectation of new treatments which are in basic research and some of them in clinical research, as can be seen in the clinical trials portal with more than 2,520 different studies[16].

In this review we aim to try to identify in a general way the pharmacological treatment currently existing and what is being investigated in these genetic diseases. The way in which a therapeutic approach is carried out is focused on one of the points of the pathophysiological cascade of genetic diseases. Thus, treatment could be at the level of the affected gene(s) (e.g. gene and chromosome therapy), replacing the abnormal protein (e.g. hematopoietic cell transplantation), modifying the metabolic cascade (e.g. special formulations, substrate reduction therapy) and symptomatic[17] (Figure 1).



Fuente: Sphingolipid lysosomal storage disorders[17]

Figure 1. Therapeutic approach to genetic diseases. Some genetic conditions may involve one or more of any of these links. For example, phenylketonuria can be managed by decreasing the amount of substrate (phenylalanine) through special formulas or enzyme replacement therapy. Source: Sphingolipid lysosomal storage disorders (17).

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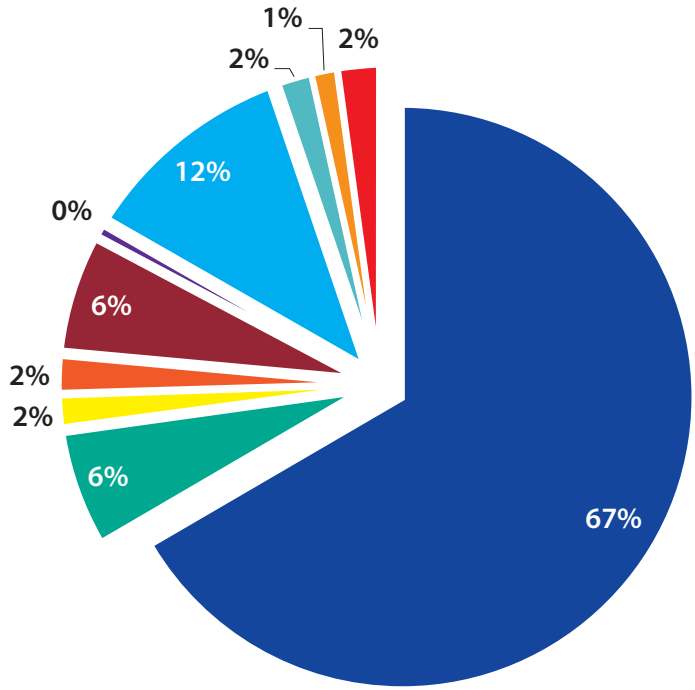
GENE THERAPY

The main objective of gene therapy (also known as gene therapy) is to sufficiently incorporate a long-lasting expression of a therapeutic gene or transgene in order to improve or cure symptoms with minimal adverse events[18].

When research began, it focused mainly on monogenic diseases. However, currently most clinical research studies are directed at cancer[19] (Figure 2).



Source: Gene Therapy Clinical Trials Worldwide[19]

Figure 2. Proportion of diseases using gene therapy in clinical trials. Genetic diseases are the second most frequently investigated group of conditions. Source: Gene Therapy Clinical Trials Worldwide (19).

The types of gene therapies are directed to germ cells (sperm or egg cells) or somatic cells. The duration of the expression of the transferred gene depends on the type of pathology, for example, in monogenic diseases the time should be prolonged, while in multifactorial diseases (e.g. cancer, infectious diseases) it should be short[20].

There are two types of gene transfer: in-vivo and ex-vivo[21]. The former means that the gene is delivered directly to a tissue, while in the latter, cells are extracted from the patient, the gene is delivered and then incorporated back into the affected individual[18,21]. The types of gene therapy can be subdivided into those using virus-mediated therapy and nanoparticles, synthetic short nucleotides, as well as gene editing[22].

VIRUS-BASED THERAPIES

The most frequently used viruses are: adenovirus, adeno-associated viruses, lentivirus, retrovirus[23,24] (Figure 3). Adeno-associated viruses are the most commonly used because they have a greater capacity to infect different tissues and have a lower inflammatory response[20].

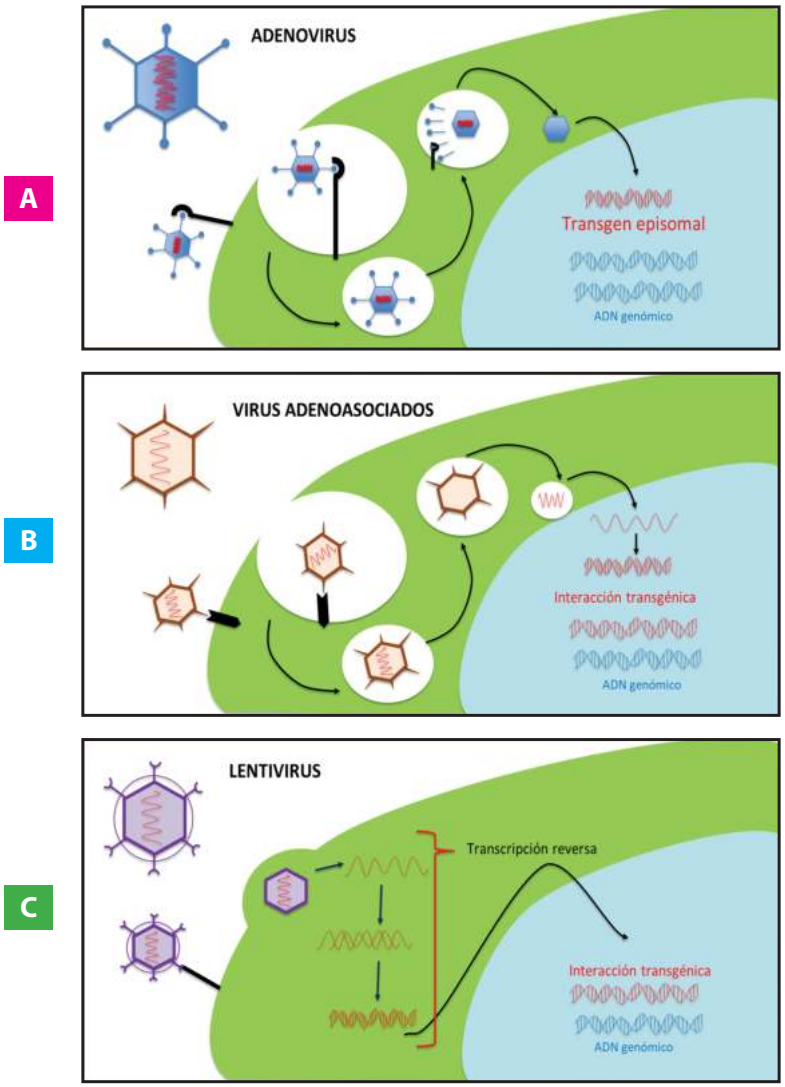


Figure 3. A. Adenoviruses. They are constituted by a double stranded (double stranded) DNA, after "infecting" the host cell, the genetic material is not incorporated into the genetic material of the host (Episome). B. Adenoassociated viruses. Constituted by a single-stranded DNA, and after infection of the host cell, the genetic material is not incorporated into the host genome. C. Lentivirus. They are a subtype of retroviruses (RNA) derived from human immunodeficiency viruses, after the incorporation of RNA into the host cell, this RNA uses a complex reverse transcription machinery to produce double-stranded DNA. This double-stranded DNA is then incorporated into the host genome.

Since 2016 to date, virus-based genotherapies have been approved (by FDA and EMA), which we mention below[18,25]:

a. Alipogene tiparvovec -Glybera- is an adeno-associated virus (AAV1) used for hyperlipoproteinemia type 1 (MIM #238600) caused by recessive variants of the LPL gene, leading to lipoprotein lipase deficiency, causing hyperchylomicronemia and pancreatitis[26].

b. Strimvelis, uses a retrovirus as a vector, which is used in adenosine deaminase deficiency (ADA gene), characterized by severe combined immunodeficiency (MIM #102700)[27].

c. Zynteglo, using a lentivirus as a vector, is used in beta-thalassemia (MIM #613985), characterized by congenital hypochromic microcytic anemia, decreased hemoglobin (Hb) A and increased Hb F, hepatosplenomegaly[28].

d. Voretigene neparvovec-rzyl -Luxturna- (AAV2), approved for the use of recessive variants of the RPE65 gene that causes Leber congenital amaurosis (MIM #204100) and retinitis pigmentosa 20 (MIM #613794)[29].

e. Onasemnogene abeparvovec-xioi -Zolgensma- (AAV9), which is used for spinal muscular atrophy 1 (MIM #253300), who are children presenting progressive congenital hypotonia, where the majority of those affected (95-98%) present a deletion in exon 7 of the SMN1 gene[30].

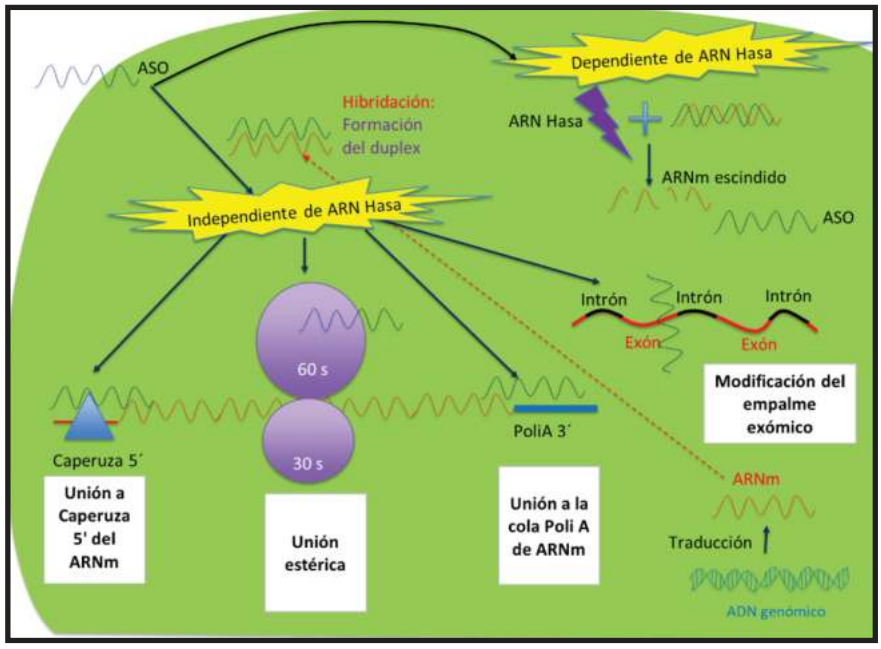
THERAPIES WITH SHORT NUCLEOTIDES

Among the therapies that use short synthetic nucleotides, there are two types:

a. Antisense oligonucleotides (AON, from antisense oligonucleotide), have 20-30 nucleotides of DNA, with two forms of action: i) using RNA Hase, in which it destroys messenger RNA (mRNA) and ii) without using RNA Hase, where it can act by modulating splicing, through steric blocking, binding to the 5' cap region of mRNA or the 3' poly A region[22,31-33] (Figure 4A).

b. ARN de interferencia (ARNi), se utilizan como mecanismo de defensa natural contra los virus ARN. El mecanismo de acción es mediante la utilización de los complejos moleculares Dicer (ribonucleasa) y RISC (del inglés, RNA-induced silencing complex), uniéndose de manera complementaria al ARNm y su posterior rompimiento[22,31-33] (Figure 4B).

A



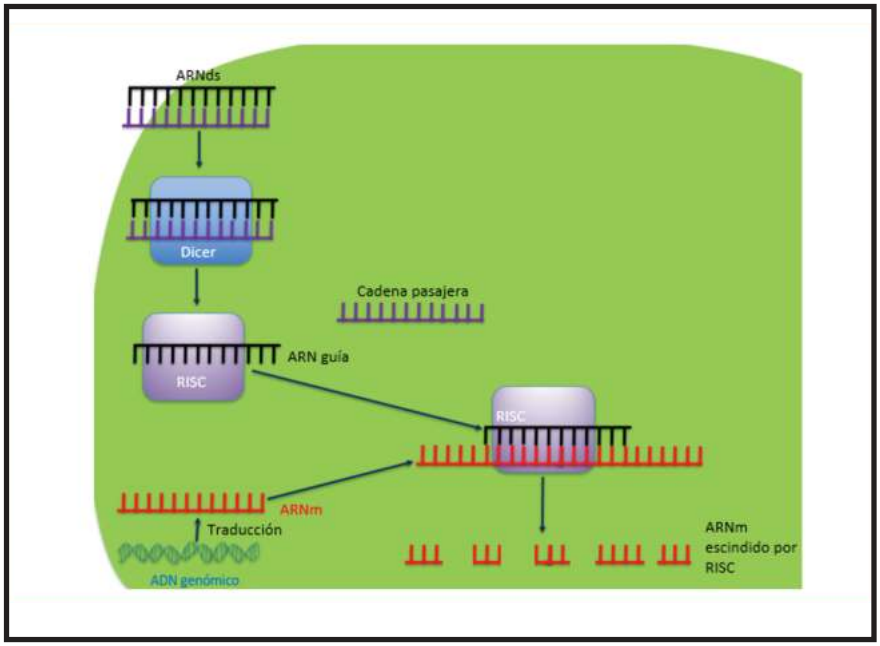


Figure 4. Mechanisms of action of short nucleotides A. Used by OAS to alter messenger RNA (mRNA). B. Employed by RNA interference (RNAi).

To date, we have the following molecules approved by the FDA and/or EMA:

a. Eteplirsen: is an AON used in patients with Duchenne muscular dystrophy (MIM #310200) and who present the deletion of exon 51 of the DMD gene; causing a skipping of this exon resulting in a short protein, however, with greater functionality[34,35].

b. Nusinersen: is an AON used in spinal muscular atrophy type 1 (MIM #253300), which is caused by homozygous variants of the SMN1 gene. This AON is used in patients who have at least one copy of the SMN2 gene, modifying the expression of the SMN2 gene (which is usually decreased), being a protein similar to SMN1[36-38].

c. Paitisiran: is an RNAi used in transthyretin-related hereditary amyloidosis (MIM #105210), caused by heterozygous monoallelic variants in the TTR gene. This RNAi causes the reduction of the "mutant" protein[39].

d. Mipomersen: is an AON used in familial hypercholesterolemia (variants in the LDLR, APOB, PCSK9 genes)[40].

GENETIC/GENE EDITION

On the other hand, it is of utmost importance to know that greater possibilities are opening up with the use of gene editing through meganucleases, nucleases such as ZNF (zinger nuclear finger), TALE (transcription activator-like repeat) and CRISPR/Cas9 (clustered regularly interspaced short palindromic repeat / CRISPR associated protein 9). The latter system is based on a system found in bacteria and archae, which confers resistance to viruses. CRISPR/Cas 9 contains two elements, an endonuclease (Cas 9) and a simple guide sequence (sgRNA) (Figure 5A). Uses range from gene regulation (Figure 5B-5E), epigenetic modification to genome imaging. Monogenic diseases under basic research include congenital cataract, Duchenne muscular dystrophy, hereditary tyrosinemia type 1, cystic fibrosis, betatalasemia, urea cycle disorders[41].

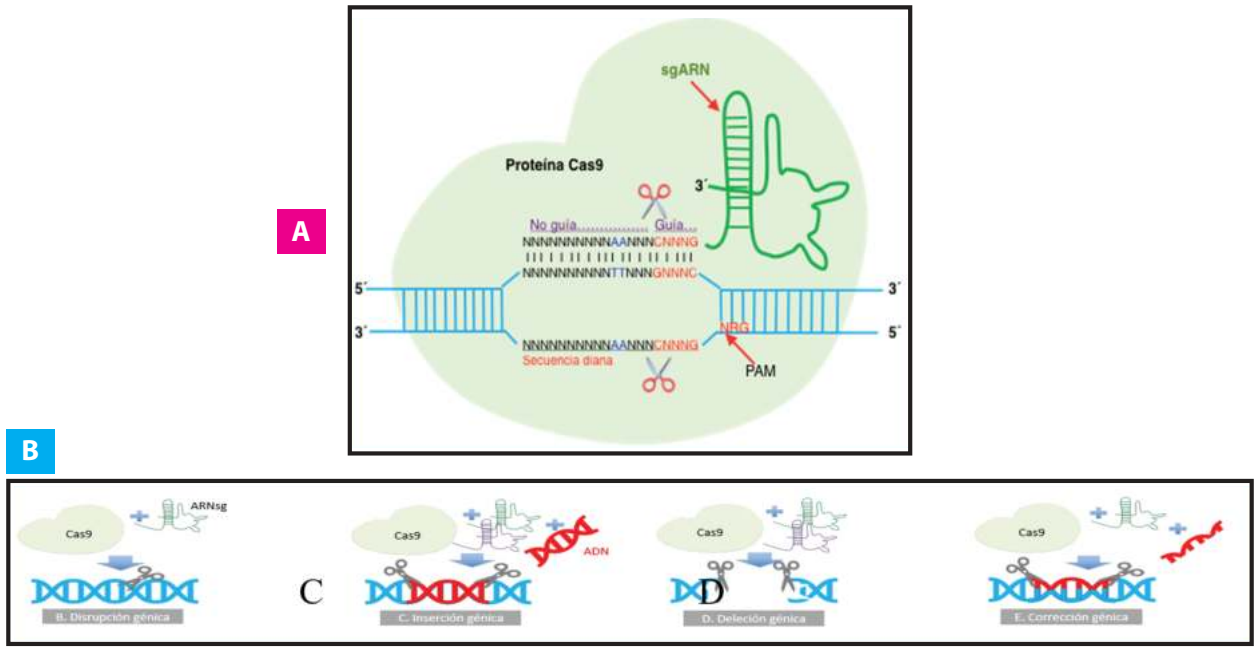


Figure 5. CRISPR/Cas9 A. CRISPR/Cas9 system. PAM= protospacer adjacent motif, N=A, R=G or A. = Cas9 protein. Sg=single guide. Mechanisms of action of the CRISPR/Cas9 system. B. Cas9 and sgRNA cause gene disruption (knock out). C. Cas9, two sgRNAs plus one DNA strand insert a gene (knock in). D. Cas9 and two sgRNAs deletes a gene. E. Cas9, sgRNA and a DNA template correct a genetic variant ("mutation").

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GENE THERAPY USING NON-VIRAL VECTORS

These are research strategies that have the possibility of incorporating DNA through synthetic vectors, which are frequently known as nanoparticles (NPs) measuring 10 to 500 nm[23]. These NPs have the advantage of very easy synthesis, lower production costs than viral vectors, greater safety, the capacity to transport larger molecules and greater efficacy[23]. These nanoparticles can be composed of polysaccharides, solid lipids or coated with CK30PEG (30-mer cationic polylysine conjugated with 10KDa polyethilene glycol)[23]. On the other hand, the incorporation of DNA is being tested with the use of a vector ("naked" DNA) by means of physical methods such as electroporation, sonoporation, magnetofection and "bullet" genes[20].

NUTRITIONAL THERAPY

This type of therapy is mainly used for inborn errors of metabolism (IEM)[42]. It is important to emphasize that there are at least 81 pathologies that, with early diagnosis and timely treatment, will prevent the risk of intellectual disability (www.treatable-id.org)[43]. It is of utmost importance to emphasize that the ideal moment of diagnosis is as early as possible, and if possible through universal neonatal screening of at least the most frequent entities[44]. We can divide this type of therapy into[45,46] (Table 1):

a. Nutrient restriction

   When it is known that there is an increase in a toxic metabolite due to a decrease in enzymatic activity, and that there are other metabolites cascading above; what is done is to reduce these through special formulas, causing the toxic to decrease, thus avoiding the onset of the pathophysiological cascade[47,48].

b. Nutritional supplementation

   In many cases, apart from nutrient restriction with special formulas, it is necessary to supplement with metabolites that are not adequately produced[45,46].

c. Elimination or blocking of toxic metabolite synthesis

   There are many IEM, where the pathophysiology of the picture is mainly framed in the alternative production of a toxic metabolism, so it is necessary to use drugs or procedures (e.g. the use of hemofiltration in urea cycle defects) that eliminate or block the synthesis of these[45,46].

Table 1. Management of some inborn errors of amino acid, carbohydrate and lipid metabolism.

Disease	Clinical features without timely treatment	Enzyme deficiency	Mim o ps	Special formulation	Supplementation, dietary, considerations and other treatments	References
			Aminoácidos			
Phenylketonuria	Phenylalanine, profound and irreversible intellectual disability.	Phenylalanine hydroxylase	261600	phenylalanine and tyrosine	L-tyrosine, long neutral amino acids, tetrahydropterin	47, 48
Hyperphenylalaninemia, BH4 deficiency	Phenylalanine.Do not respond adequately to special formulations with FA , RDPM, DI, axial hypotonia and appendicular hypertonia, epilepsy.	Dihydropteridine quinoid reductase	261630	phenylalanine and tyrosine	Tetrahydropterin: 2mg/kg	48
Tyrosinemia Ia, Ib	Succinylacetone, tyrosine, FA, methionine. Severe liver disease, renal tubular disorder, rickets.	Fumarylacetoacetate	276700	phenylalanine and tyrosine	NTBC 1-2 mg/kg/day	49
Tyrosinemia II	Tyrosine , normal FA. Herpetiform corneal ulcers and punctate keratosis of fingers, palms and soles, DI.	Tyrosine transaminase	276600	phenylalanine and tyrosine	3-omega fatty acid supplementation	50
Maple syrup-colored urine disease	↑Leucine, ↑isoleucine, ↑valine. Matchstick maple syrup odor, neonatal encephalopathy.	Dihydrolipoamide branched-chain transacylase, BCKA beta-subunit decarboxylase, BCKA alpha-subunit decarboxylase.	248600	Leucine	Oral thiamine: 100-300 mg/day. L-Valine, L-isoleucine	50
Isovaleric acidemia	Isovalerylacidemia, metabolic acidosis, RDPM, epilepsy, cerebral hemorrhage, neutropenia, leukopenia, pancytopenia.	Isovaleryl CoA dehydrogenase	243500	Leucine	L-carnitine: 100 mg/kg/day. Glycine 200-400 mg/kg	51

3-OH-isobutyric aciduria	Organic acidemia, lactate↑, 3-OH-isobutyric aciduria.	Defects of the respiratory chain or defects of methylmalonate semialdehyde dehydrogenase.	236795	↓valine	L-carnitine: 100 mg/kg/day.	52
3-Methylglutaconic aciduria	3-methylglutaconic aciduria. In type 1, lack of medro, optic atrophy, spastic quadriplegia, dystonia, hyperreflexia, 3-methylglutaconic aciduria are observed.	9 different enzymes	PS250950	↓Leucine	L-carnitine: 100 mg/kg/ day. Glycine 250-400 mg/ kg/day. Pantontenic acid: 15-150 mg/day.	53
Homocystinuria	Homocysteine↑, ectopia lentis, RDPM, DI	Cystathionine β-synthase	236200	↓methionine and ↓cysteine	Folic acid: 500-1000/ mg/ 3 times per day. Betaine: 150 mg/day. Pyridoxine 25-750 mg/day. B12 1 mg (IM), 10-20 mg (oral).	54
Glutaric acidemia type 1	Glutaric acid↑, glutaconic acid↑. Acute encephalopathy, macrocephaly, basal ganglia lesions.	Glutaryl CoA dehydrogenase	231670	↓lysine and ↓tryptophan	Riboflavin: 100-300 mg/ day.	55
Lysinuric protein intolerance	Lysine↓. Recurrent vomiting, diarrhea, coma episodes, aversion to protein-rich foods, hepatomegaly and muscular hypotonia.	SLC7A7 (solute carrier familiy 7, member 7)	222700	↓protein intake	L-citrulline: 2.5-8.5 g/day in 4 doses.	56
Propionic and methylmalonic acidemia	Acute deterioration, metabolic acidosis, ammonium↑. Early death or neurologic disorder, chronic renal disease, cardiomyopathy.	Methylmalonyl CoA-mutase and propionyl CoA carboxylase	606054 y 251000	↓methionine, isoleucine, threonine, valine	Biotin: 5-10 mg/day. B12 10-20 mg/day. L-Carnitine: 100 mg/kg/day.	57

Urea cycle disorders	Ammonium↑↑↑, in cases with severe enzyme deficiency, lethargy, anorexia, hyper- or hypoventilation, consvulsions and coma are observed. In cases with mild deficiency, ammonium is elevated due to a trigger (acute illness or stress), with loss of appetite, vomiting, lethargy, delusions, hallucinations, psychosis and acute encephalopathy.	Carbamoyl phosphate synthetase I, ornithine transcarbamylase, argininosuccinic acid synthetase, argininosuccinic acid lyase, arginase, N-acetyl glutamate synthetase, ornithine translocase, citrinase.	Heterogeneous	□amino	L-arginine: 200-400 mg/kg. L-citrulline: 200-400 mg/kg/day. Sodium benzoate: 250-500 mg/kg/day, hemofiltration and hemodialysis with ECMO, carbamyl glutamate.	58
			Carbohydrates			
Classic galactosemia	Galactose 1-phosphate↑. Swallowing problems, failure to thrive, hepatocellular damage, bleeding, E. coli sepsis, RDPM, language disorder, premature ovarian failure, cataract.	Galactose 1-phosphate uridylyltransferase	230400	Eliminate galactose (lactose, galactolipids)	Soy milk. Elemental calcium	59
Glycogenosis type I	Hepatomegaly, nephromegaly, hypoglycemia, lactic acidosis, uric acid↑, lipids↑, triglycerides↑, seizures. "Doll" facies, short stature, chronic neutropenia, xanthoma, diarrhea.	Glucose 6-phosphatase or glucose 6-phosphate transporter	232200	Eliminate lactose, fructose, sorbitol	Compound carbohydrates: raw starch (1.5-2 g/kg/dose). Dietary fractionation	60
Hereditary fructose intolerance	Glucose, lactic acidemia, phosphorus ↓, uric acid ↑,, magnesium ↑, alanine↑. Nausea, vomiting, lack of medro, acute lethargy, convulsions, coma. Hepatic and renal failure.	Fructose 1-phosphate aldolase	229600	□Fructose <10 mg/kg	Vitamin C	61
			Lipids			
Long-chain fatty acid oxidation defects	Hypoglycemia, ketones↓↓↓, insulin ↑ free fatty acids↓. Cardiomyopathy, myopathy.	Cationic organic transporter 2, carnitine palmitoyltransferase type 1A and 2, carnitine-acylcarnitine translocase, VLCAD, mitochondrial trifunctional protein	Heterogeneous	□Lipids: 15-20% of total calories	L-carnitine: 100 mg/kg. Dietary fractionation. MCT: 30% of total lipids, DHA	62

FA= phenylalanine, RDPM= psychomotor developmental delay, DI= intellectual disability, NTBC=, ECMO=extracorporeal membrane oxygenation. VLCAD= very long chain acyl-CoA dehydrogenase.

HEMATOPOIETIC CELL TRANSPLANTATION

Known as hematopoietic stem cell transplantation (HSCT), which is widely used in different genetic diseases. This type of therapy is available and proven effective for primary congenital immunodeficiencies (e.g. Duncan disease), osteogenesis imperfecta and lysosomal storage diseases (LSD) (Figure 6), such as X-linked adrenoleukodystrophy, mucopolysaccharidosis I, II, VI and VII; metachromatic leukodystrophy, fucosidosis and mannosidosis[64-67].

The rationale for applying HSCT in lysosomal storage diseases (LSD) is based on the ability of transplanted cells and/or their cell progeny (or clones) to contribute to the macrophage populations of affected tissues and thus become permanent local sources of functional lysosomal enzymes; in this way metabolically active cells can improve the disease phenotype by removing storage material and modulating local inflammation at diseased sites. Cell turnover with the donor after transplantation is supposed to affect all types of tissue-bound myeloid populations, including myeloid cells and possibly microglia in the brain. For this reason, HSCT was intended as an avenue for treating enzyme-deficient patients with severe central nervous system (CNS) involvement. Importantly, if complete donor chimerism is achieved, HSCT is a unique intervention capable of providing a lifelong source of enzymes for the affected patient. The donor cells also re-establish a new immune system in the patient, overcoming pre-existing ones and preventing post-treatment immune responses directed at the functional enzyme. On this basis, since the first LSD patients were transplanted in the early 1980s, a few thousand LSD patients have been treated with allogeneic HSCT over the past decades[68]. (Figure 6).

It is of utmost importance that the effectiveness of therapy will depend to a greater or lesser degree as long as the patient is asymptomatic or minimally affected[65,66].

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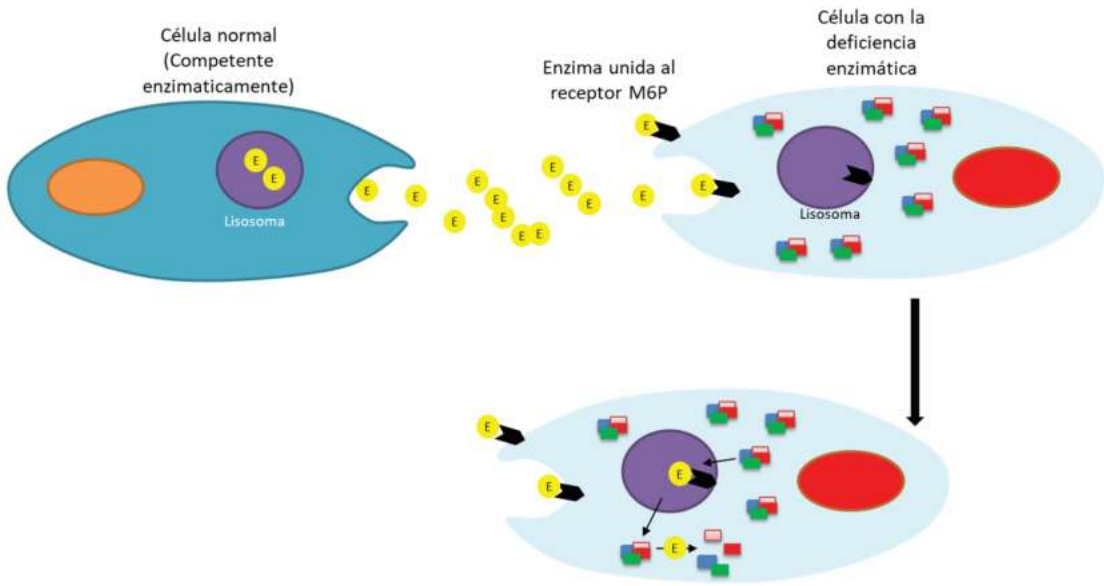

Figure 6. Mechanism of action of hematopoietic cell transplantation. The donor cell will synthesize the deficient enzyme (E), which will be captured by the deficient cells, through the 6-phosphate mannose receptor (M6), integrating this complex into the lysosome to subsequently degrade the metabolic complexes.

ENZYME REPLACEMENT THERAPY (ERT)

There are many pathologies of genetic origin that by delivering the defective protein will change the natural history of the disease. Within this group of entities are lysosomal depot diseases and adenosine deaminase deficiency[69-78] (Table 2).

Table 2. Enzyme replacement therapy in genetic diseases.

ntity	MIM	Affected gene	Main clinical characteristics	Approved TRE (FDA and/or EMA)	References
Mucopolysaccharidosis I	607014, 607015, 607016	IDUA	Coarse facies, macrocephaly, skeletal dysplasia, hepatosplenomegaly, variable neurological involvement, pulmonary and cardiac involvement, progressive joint contractures, corneal opacity.	Laronidase	74,75
Mucopolysaccharidosis II	309900	IDS	Coarse facies, macrocephaly, skeletal dysplasia, hepatosplenomegaly, variable neurological involvement, pulmonary and cardiac involvement, progressive joint contractures, claw hand.	Idursulfase Hunterase	74,75 78
Mucopolysaccharidosis IV A	253000	GALNS	Coarse facies, skeletal dysplasia predominantly thoracic, pulmonary and cardiac involvement, corneal opacity, hyperlaxity in hands.	Elosulfase alfa	74,75
Mucopolysaccharidosis VI	253200	ARSA	Coarse facies, macrocephaly, skeletal dysplasia, hepatosplenomegaly, pulmonary and cardiac involvement, progressive joint contractures, claw hand.	Galsulfase	74,75
Pompe Disease	232300	GAA	Progressive loss of muscle strength, at birth can be observed as hypotonia and cardiomegaly.	Alglucosidase alfa	70
Gaucher Disease	230800	GBA	Thrombocytopenia, splenomegaly, bone involvement.	Imiglucerase Velaglucerase Taliglucerase	81

Fabry Disease	301500	AGA	Acroparesthesias, angiokeratomas, chronic renal disease, cardiac involvement, cornea verticilata,	Agalsidasealpha Agalsidase beta	69,79
Hypophosphatasia	241500, 241510	ALPL	Decreased bone and dental mineralization. Variable presentation from pathological fractures, chondrocalcinosis, "myopathy", early loss of deciduous teeth, short stature.	Asfotase alpha	73
Lysosomal acid lipase deficiency	278000	LIPA	Malnutrition, hepatomegaly with hepatic failure, calcification of the adrenal glands. Cholesterol ester deposition disease. Cirrhosis, hypersplenism, intestinal malabsorption.	Sebelipase alfa	76
Adenosine deaminase deficiency	102700	ADA	Severe combined immunodeficiency due to accumulation of toxic metabolites causing malfunction and formation of lymphocytes.	PEG-ADA	70
Phenylketonuria	261600	PAH	Used in adult patients with phenylketonuria.	Pegvalase	77
Neuronal ceroid lipofuscinosis type 2	204500	TPP1	Onset at 2-4 years of age with epilepsy, neuroregression, myoclonic ataxia, pyramidal signs, visual impairment (4-6 years of age).	Cerliponase alpha	

CHAPERONAS

Migalastat is currently approved for use in Fabry disease (MIM #301500). Chaperones have the function of stabilizing the usual activity of a protein[79].

TERAPIA DE REDUCCIÓN DEL SUSTRATO

Substrate reduction therapy consists of reducing the metabolite(s) one step upstream of the affected pathway. Miglustat and eliglustat are held as therapeutic weapons for diseases such as Gaucher 1 (MIM # 230800) and Niemann-Pick type C (MIM #257220)[80–82]. There are many reviews that genistein has this mechanism of action in mucopolysaccharidoses (e.g. type III)[83].

CHROMOSOME THERAPY

Se encuentra en investigación básica y se basa en mejorar el efecto de las duplicaciones o deleciones parciales o totales. Dentro de las estrategias utilizadas se tiene[84,85]:

Silenciamiento de cromosomas con XIST, el cual consiste en utilizar nucleasas (ej. ZNF) para insertar una forma inducible del gen XIST en una de las copias en las células trisómicas (Figure 7A).

a. Positive-negative selectable markers on the extra chromosome; the thymidine kinase-neomycin (TKNEO) transgene is used, which helps to select with antibiotics and then isolate disomic cells from a trisomic population. The fully trisomic cells (iPSCs-inducible pluripotent stem cells) are infected with an adeno-associated viral vector (AAV) containing a TKNEO transgene that confers neomycin (NEO) resistance and sensitivity to ganciclovir. Due to imperfect efficiency, only some cells in the population receive the TKNEO transgene. The cell population is treated with neomycin, after which the cells that do not contain the TKNEO transgene are removed. The population containing the pure transgene is proliferated to allow nondisjunction events to occur naturally. The cohort of disomic and trisomic cells is then treated with ganciclovir (GCV); all trisomic and TKNEO transgene-containing cells are removed leaving only the pure disomic population that can be isolated and proliferated (Figure 7B).

b. Drug-induced trisomic rescue; where trisomic cells (trisomy 21 and 18) are cultured with ZSCAN4, which increases the number of euploid (normal) cells by 24%.

c. Artificial human chromosomes (HAC-human artificial chromosomes); known as minichromosomes, which are used as "vectors". These are freely integrated into the cell cycle over time, which would have the possibility of correcting deletions.

d. Induction of ring chromosome formation. In trisomic cells (iPSCs) LoxP is inserted into the short and long arm of the chromosome through CRISPR-Cas9. Then the cells are treated with a recombinase that induces the formation of ring chromosomes, then these cells replicate and lose the ring chromosome naturally, restoring the disomic state.

e. Inhibition of the DYRK1A gene, it has been demonstrated that this gene is involved in the physiopathology of the intellectual disability of Down syndrome. One of the drugs that has demonstrated its efficacy and safety in adult patients (phase 2) with Down syndrome is epigallocatechin-3-gallate (green tea extract), improving cognition, visual recognition memory, inhibitory control and adaptive behavior[86,87].

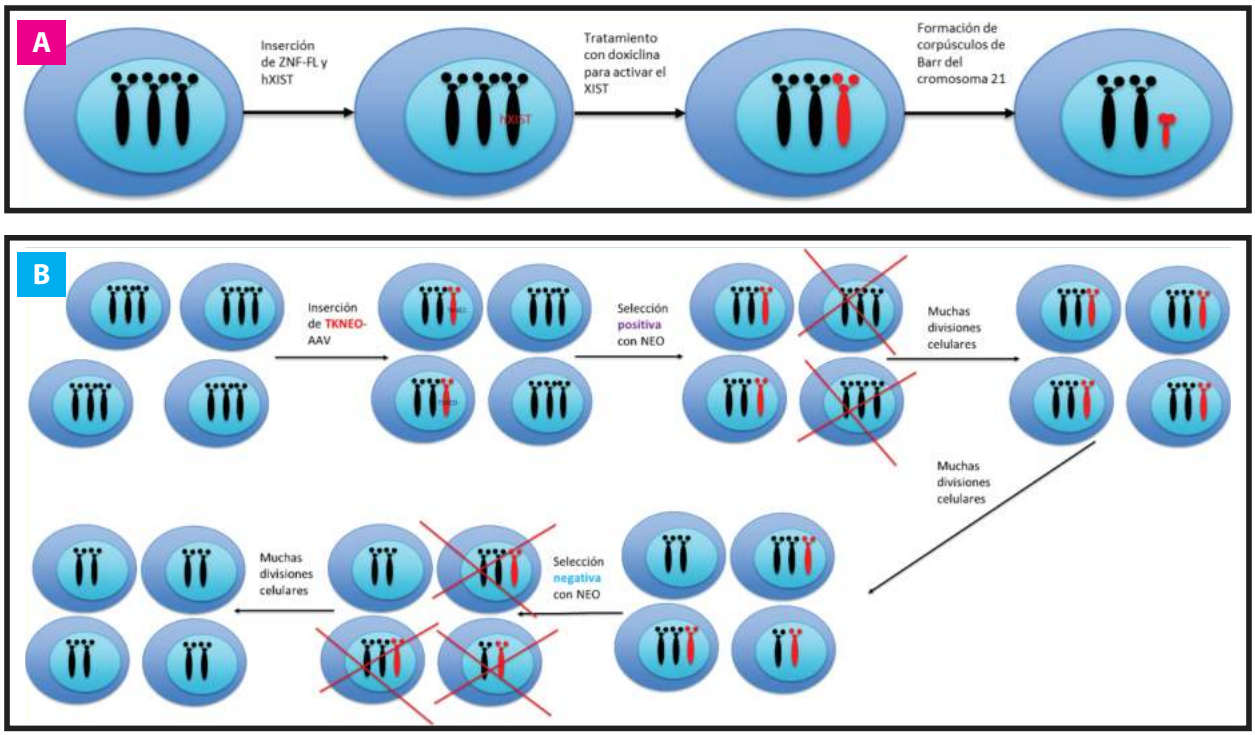

Figure 7. A. Silencing of aneuploid chromosomes by inserting XIST. In trisomic cells (iPSCS) the XIST (red) is incorporated into one of the chromosomes by ZNF, then the cells are treated in order to activate (transcribe) the XIST, thus silencing the entire extra chromosome (red), which is subsequently observed as a Barr corpuscle, re-establishing a "disomic" state. B. Use of selectable positive-negative markers on the extra chromosome.

OTHER THERAPIES

Some monogenic diseases currently have therapies under clinical investigation, which could be verified at www.clinicaltrials.com.

Some of the therapies shown are probably not directly focused on what is described in Figure 1; however, they have been shown to have enormous utility in the management of these diseases.

Duchenne muscular dystrophy (DMD) is a pathology manifested by progressive loss of muscle strength in the first decade. Three therapies are currently available, one of them we mentioned in short nucleotide therapies, and the others are the use of deflazacort and ataluren. Deflazacort has been widely used in DMD for more than 30 years; however, it was only approved by the FDA in 2017[88].

Ataluren is used in those patients who have a nonsense variant (10-15% of DMD patients). Its mechanism of action is to perform a reading jump at the site of the nonsense variant, making the protein larger than the "mutated" protein. In this way it causes the phenotype to change to Becker muscular dystrophy[89].

In this same sense, the use of bisphosphonates in diseases such as osteogenesis imperfecta (PS166200) and McCune-Albright syndrome (MIM #174800) are indicated to reduce pain and the risk of the appearance of fractures[90,91].

Other therapies in osteogenesis imperfecta that have been observed to decrease the risk of fractures is through the activation of osteoclasts (denosumab), bone anabolic agents (teriparatide, romosozumab)[67].

X-linked hypophosphatemic rickets (MIM #307800) is a condition in which chronic hypophosphatemia is observed which causes a failure in mineralization leading to rickets and osteomalacia. A monoclonal FGF23 inhibitor (burosumab) has been shown to be a promising therapy in this condition[92].

Tuberous sclerosis (MIM #PS191100) has very heterogeneous clinical manifestations and the FDA has approved the use of mTOR inhibitors such as everolimus for epilepsy, rhabdomyosarcomas, astrocytomas, angiomyolipomas; and rapamycin for lymphangioleiomyomatosis[93].

CONCLUSION

The pharmacopoeia in genetic diseases is increasing notably over time. Many therapies try to be very specific; however, drugs are being developed that will be used in more than one entity, which are even etiologically unrelated.

As we are seeing in recent years, these new therapies are changing the natural history of this group of entities. However, the bottleneck in these conditions is diagnosis, either due to the limited number of specialists, lack of implementation, high costs, insurance coverage, among others.

The future of medicine in general is conditioned to better understand the underlying and inherent mechanisms of each disease, based on an individual understanding of our "omics", thus taking it to another level of medicine: Precision Medicine.

Finally, it is important to indicate that all these therapies and drugs are promising and valuable therapeutic options for these different diseases described; however, it is of utmost importance that the management of all these conditions is multi and interdisciplinary and carried out by qualified professionals within laboratories and institutions properly certified for these purposes.

REVIEW ARTICLE

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