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Review Article

Genetic Disorders in Premature Aging Diseases

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Abstract

Children and teenagers display some rare but severe multifactorial genetic disorders, leading to death that remains the ultimate consequence of aging. These diseases include acrogeria, pangeria (Werner syndrome), and progeria (also known as adult progeria). Genetic disorders of the family of laminopathies have been identified in this family of disease. Cockayne syndrome, atherosclerosis, Parkinson, mandibuloacral dysplasia (MAD), Rothmund-Thomson syndrome (RTS) and Hutchinson-Gilford progeria syndrome (HGPS), a genetic pathology that promote a premature cell aging, are juvenile forms of the gene mutations. In this article, we summarize the symptoms of the different **s**ickness inducing a precocious and accelerated aging. Characteristic features affect LMNA that encodes lamins A and C. They are located on chromosome 1. The A-type lamins have important structural function in the nuclear envelope. At the present time, there is no treatment for these pathologies and young patients die from these diseases.

Keywords: Progeria utchinson-Gilford syndrome, Cockayne syndrome, Werner syndrome, Laminopathies, Genetic disorders, Accelerated aging, Death

INTRODUCTION

Age-related diseases concern mostly adults or old patients. However, some rare but severe genetic disorders are occurring on children, leading to death that remains the ultimate consequence of aging [1-12].

Examples of adult aging-associated diseases linked to genetic mutations are numerous. They include atherosclerosis and cardiovascular disease, cancer, arthritis, cataracts, osteoporosis, type 2 diabetes, hypertension and Alzheimer's disease. The incidence of these diseases increases exponentially with age.

In young patients (newborns and teenagers), aging is an extremely complex, multifactorial process. The ultimate causes of ageing remain unknown. The human cells ability to divide is limited to approximately 50-times, after that limit they simply stop dividing (Hayflick limit theory of ageing). One million persons per day die from age-related causes including:

- Age-related macular degeneration that affects eyes, which could lead to vision loss through the degeneration of the macula.
- Alzheimer ‘s disease: Treatment associating pravastatin (given for the prevention of lipidic formations inside vessels and cardiomyopathy) prescribed together with zolédronate (an amino-bisphosphate acting on osteoporosis, a specific form of the Charcot Marie-Tooth disease).

Also, rare and premature genetic disorders lead to patient diseases. The number of cases per mutation is reduced but reach in most time severe forms. Three forms of premature genetic disorders have been identified in newborn and children:

- ✓ Acrogeria (Gottron sickness) affecting girls with an atrophic skin, and associated with telangiectasy and hyperpigmentation.
- ✓ Pangeria (Werner syndrome), characterized by gray hairs, stop growth, atrophy cutaneous diffuse, sclerosis from extremities, keratosis and hyperpigmentation cataracts of the two eyes, skin ulcers, type 2 diabetes, hardening of arteries, thinning of bones, for a total of 1 for 1,000 000 individuals (1 for 200 000 according other data). Autosomal recessive mutation of the WRN gene were identified in this disease.
- ✓ Progeria cranial malformations, of the face and ungula distortions, loss of hairs, skin pigmented and sclerotic.

Premature aging constitutes severe syndromes. These pathologies referred to genetic disorders of the family of laminopathies. They include Cockayne syndrome (also called Neill-Dingwell syndrome), Werner syndrome (WS), progeria, atherosclerosis, Parkinson, and others sickness. Cancer and stroke are also in the list of laminopathies. Differential diagnoses include mandibuloacral dysplasia (MAD), Rothmund-Thomson syndrome (RTS) and Hutchinson-Gilford progeria syndrome (HGPS;). Type 2 diabetes mellitus also share similarities with WS.

- Mandibuloacral dysplasia (MAD)
- Partial lipodystrophy

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- Rothmund-Thomson syndrome (RTS) should also be added to the list of diseases.

Forms of premature aging are the following:

Werner syndrome (known as adult progeria), lipodystrophy-atypical Werner dysplasia, muscular dystrophy of Emery-Dreifuss, belt myopathy of the 1B type, involving muscle perturbations, neural, osseous or dermal alterations, cardiomyopathy associated to a specific form of the Charcot Marie-Tooth disease. The family of genetic premature diseases disorders is linked to the influence of the aging process. The different forms of pathology: acrogeria, pangeria, progeria, Cockayne 'syndrome, xeroderma pigmentosum, scleroderma leads to premature genetic-disorders, most of them being autosomal recessive, leading to death.

THE LAMINOPATHIES FAMILY

Cockayne syndrome, also called Neill-Dingwell syndrome, provide significant evidence of premature aging. The patient is sensitive to light, has a short stature (dwarfism, and progressive dementia). Two to 3 patients per one million newborns are identified as bearing this syndrome. Eyes (cataracts, strabismus), microcephaly, anhydrosis, high blood pressure, and hearing loss are also present in the list of pathologic dysfunctions. The mutation of the ERCC6 or ERCC8 genes is significant in this context. Regular checkups are necessary to prevent and treat tooth decay. This syndrome is due to a protein misfolding. Beta-amyloid and hyperphosphorylated tau protein form extracellular plaques.

Life expectancy is less than 10-20 years. A number of rare genetic sickness induces a precocious and accelerated aging. It is the case of the Cockayne syndrome, (2,5 cases per one million births in association with a life spam less than sept years for the most severe form). Children affected by this sickness get older more rapidly than expected They lose weight, hairs are lost, hearing and vision decrease. This pathology leads to a neurodegenerescence and facial alterations.

Due to the mutation of the two genes, defects of cells of patients having an enhanced production of one enzyme HTRA3 degradation of one enzyme synthetized by mitochondria leads to cell degeneration. Partial lipodystrophy A includes a number of rare genetic **s**ickness and the mutation induces a precocious and accelerated aging.

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Werner syndrome (WS) Is a member of the family of laminopathies. In a series of individuals aged between 1 and 100 years and mutation-proven, 40 patients were indicated as normal aging-associated elevations of highly sensitive C-Reactive Protein [CRP (hsCRP] and matrix metalloproteinase-9 (MMP-9). To further study the contribution of environmental factors such as persistent herpes viral infection to inflammageing, IgG antibodies against varicella/zoster virus (VZV) and cytomegalovirus (CMV) were examined in the same serum samples as has been done for hsCRP and MMP-9 analyses. The mean levels of serum IgG viral antibodies were comparable between normal (mean ± SE: 31.0 ± 4.3 unit) and WS (38.6 ± 7.6) for CMV, and between normal (42.0 ± 12.2) and WS (29.8 ± 3.8) for VZV, respectively. Aging-associated change of IgG anti-CMV antibody titer in WS increased significantly (1.32 times higher) compared with normal aging (p = 0.037). Elevated hsCRP level was significantly associated with IgG anti-CMV (p = 0.016) and IgG anti-VZV (p = 0.008) antibodies in normal aging, but not in WS. Serum MMP-9 was significantly associated with IgG anti-CMV level (p = 0.0002) in normal aging, but not in WS.

PROGERIA OR SYNDROME OF HUTCHINSON-GILFORD

It is obvious that the gene mutation affects premature cell aging. Newborns and young patients are altered by this pathology. Progéria is a genetic pathology that promote a premature cell aging. Its concern sickness resulting from the mutation of the gene called LMNA, that are members of the family of laminopathies. Lamins A and C, are located on chromosome 1. Mutation is occurring on a truncated protein called progerine, anchored in the membranes of the nuclei and accumulating, leading finally to dysfunctions.

A young girl aged 8 years died as a result of this genetic disease. Her pound was 7,7 kilos at 8 years, whereas her biological age was about 80 years. The pathology called progéria or Hutchinson-Gilford syndrome, affect about 160 patients in the whole world. Starting between 18 months and 24 months after birth, the first symptoms appear at this early post-natal stage. The whole life spam was a mean of 12-13 Years. Children are dying from vascular accidents of the brain (AVC) or from atherosclerosis**.** The Hutchinson-Gilford syndrome comes from the mutation of a gene, the LMNA located on chromosome 1. Unfortunately, it is not possible to have any control on the mutation and it is unpredictable. The sick patients are not "at risk", and no prevention is possible.

Progeria or Hutchinson-Gilford progeria syndrome (HGPS) is a rare, fatal, displaying genetic condition of childhood with striking features resembling premature aging. Children with progeria usually have a normal appearance in early infancy. At approximately nine to 24 months of age, affected children begin to experience profound growth delays, resulting in short stature and low weight. They also develop a distinctive facial appearance characterized by a disproportionately small face in comparison to the head; an underdeveloped jaw (micrognathia); malformations and crowding of the teeth; abnormally prominent eyes; a small nose; and a subtle blueness around the mouth. In addition, by the second year of life, the scalp hair, eyebrows, and eyelashes are lost (alopecia), and the scalp hair may be replaced by small,

downy, white or blond hairs. Additional characteristic features include generalized atherosclerosis, cardiovascular disease and stroke, hip dislocations, unusually prominent veins of the scalp, loss of the layer of fat beneath the skin (subcutaneous adipose tissue), defects of the nails, joint stiffness, skeletal defects, and/or other abnormalities. Individuals with HGPS develop premature, widespread thickening and loss of elasticity of artery walls (arteriosclerosis), which result in life-threatening complications during childhood, adolescence, or early adulthood. Children with progeria die of heart disease (atherosclerosis) at an average age of 14.5 years. As with any person suffering from heart disease, children with progeria can experience high blood pressure, strokes, angina (chest pain due to poor blood flow to the heart itself), enlarged heart, and heart failure, all conditions associated with aging.

Progeria is caused by a change (mutation) in the LMNA gene that codes for the lamin A protein. The lamin A protein is the scaffolding that holds the nucleus of a cell together. Researchers now believe that the defective lamin A protein makes the nucleus unstable. The cellular instability appears to lead to the process of premature aging in progeria. Progeria is sporadic, very rare, autosomal dominant, deadly childhood disorder. It is one of the progeroid syndromes. Aging is a developmental process that begins with fertilization and ends up with death involving a lot of environmental and genetic factors. The disease firstly involves premature aging and then death from complications of atherosclerosis such as myocardial infarction, stroke, atherosclerosis, or heart failure. The lifespan of the patient is normally up to ten or early twenties. It is usually not inherited because a patient normally dies before the age of reproduction. The most important genetic linkage between progeria and aging is shortening of telomere ends with each replication cycle. The patients are normally observed to have extremely short telomeres. Currently, 90% of the patients are said to have de novo point mutations in the LMNA gene that substitute cytosine with thymine and have been found in individuals with HGPS. LMNA encodes lamins A and C, and the A-type lamins have important structural function in the nuclear envelope. The most common type of HGPS mutation is located at codon 608 (G608G). It could not be diagnosed at birth, but after the age of 2 years, visible, prominent symptoms can be observed. Still, lot of research is needed to solve this mystery. Hopefully, future research on HGPS would provide important clues for progeria and other fatal age-related disorders.

Clinical characteristics: Huntington disease-like 2 (HDL2) typically presents in midlife with a relentless progressive triad of movement, emotional, and cognitive abnormalities which lead to death within 10 to 20 years. HDL2 cannot be differentiated from Huntington disease clinically. Neurologic abnormalities include chorea, hyperkinesia (rigidity, bradykinesia), dysarthria, and hyper-reflexes the later stages of the disease. There is a strong correlation between the duration of the disease and the progression of the motor and cognitive disorder.

Mandibuloacral Dysplasia is an extremely rare genetic disorder characterized by underdevelopment (hypoplasia) of the lower jaw (mandible) and the collarbone (clavicle), bone loss at the ends of the fingers and toes (acro-osteolysis), skin degeneration (cutaneous atrophy), and partial lipodystrophy, a condition marked by selective loss of body fat (adipose tissue) from various areas of the body. Cutaneous atrophy and lipodystrophy may contribute to affected children having a prematurely-aged appearance (progeroid features). Lipodystrophy may be associated with clinical features of metabolic syndrome including insulin resistance, impaired glucose tolerance, and diabetes mellitus. Additional symptoms can occur as well. Two types of mandibuloacral dysplasia have been identified, type A and type B. Both types are inherited as autosomal recessive conditions. Mandibuloacral dysplasia type A (MADA) is caused by mutations of the lamin A/C (LMNA) gene; mandibuloacral dysplasia type B (MADB) is caused by mutations of the zinc metalloproteinase (ZMPSTE24) gene.

Partial lipodystrophy

This review aims to summarize the current knowledge of Familial Partial LipoDystrophy (FPLD syndromes) and to describe their clinical and molecular picture, diagnostic approaches and recent treatment modalities.

Lipodystrophies are a heterogeneous group of rare conditions characterized by the loss of adipose tissue. The most common forms are the FPLD syndromes, which include a set of disorders, usually autosomal dominant, due to different pathogen mechanisms leading to improper fat distribution (loss of fat in the limbs and gluteal region and variable regional fat accumulation). Affected patients are prone to suffering serious morbidity via the development of metabolic complications associated to insulin resistance and an inability to properly store lipids. Although no well-defined diagnostic criteria have been established for lipodystrophy, there are certain clues related to medical history, physical examination and body composition evaluation that may suggest FPLD prior to confirmatory genetic analysis. Its treatment must be fundamentally oriented towards the control of the metabolic abnormalities. In this sense, metreleptin therapy, the newer classes of hypoglycemic agents and other investigational drugs are showing promising results.

Rothmund-Thomson syndrome (RTS)

Rothmund-Thomson syndrome (RTS) is a rare genetic disorder that can affect many parts of the body. The disorder is characterized by distinctive abnormalities of the skin, sparse hair, eyelashes and/or eyebrows, small stature, skeletal and dental abnormalities, and an increased risk of cancer, especially bone cancer (osteosarcoma). Patients typically begin having signs of RTS during infancy, and the first feature to appear is a rash that starts on the cheeks and later spreads to other parts of the body. The rash gradually becomes chronic and persists for life. Other features may appear that involve other areas of the body such as the eyes, bones, teeth, and hair, and patients may often be small in size compared to their peers.

Patients are at an increased risk for developing cancer, particularly certain types of skin and bone cancer. Lifespan is generally felt to be normal in the absence of death due to cancer, although follow-up data in the published literature are limited. RTS is inherited as an autosomal recessive genetic condition. The gene defect in two-thirds of cases is due to mutations in a gene called RECQL4. For the other one-third of patients, the gene(s) involved has not yet been identified.

Neurotoxic deposits cause cognitive impairments due to the initiation of destructive biochemical pathways.

Signs include:

- Atherosclerosis induces the loss of arterial elasticity
- Benign prostatic hyperplasia is due to an enlargement of the prostate gland due to increased growth
- Parkinson's is a degenerative disorder of the central nervous system. Dementia, depression, anxiety occurs in people over 60. 1% are affected.

CONCLUSION

In this review, we summarized some of the pathologies occurring in newborn and teenagers. Premature aging associated with genetic disorders are rare diseases leading to death which remains the ultimate consequence of aging. The family of laminopathies includes 1-Cockayne syndrome, 2-Werner syndrome (WS), 3-Progeria or syndrome of Hutchinson-Gilford, 4-Mandibuloacral Dysplasia, 5-Partial lipodystrophy, 6-Rothmund-Thomson syndrome (RTS), and probably many other syndromes. These pathologies shed lights on the aging process, but still some informations are missing, especially the link between the mutation and the disease. There is also a need for specific and efficient treatments. Senolytic seems to emerge among medications [13-16].

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