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Diagnosis and Treatment of Pre-Mature Aging Disease and Conditions: A Review

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ABSTRACT:
The process of aging is natural and dynamic, taking place in all living cells, organs, and organisms. The irreversible process is considered typical until it happens within a specified timeframe. Pathological age-related conditions include syndromes like Wiedemann–Rautenstrauch syndrome, Werner syndrome, Hutchinson-Gilford Progeria Syndrome, and PYCR1-related cutis laxa. Genetic mutations are responsible for the occurrence of these syndromes, and they can be effectively managed through a combination of medicinal and genetic therapies. Several improvements have been developed to address these conditions. Since there are only a few cases, we still don't have a conclusive treatment. This literature review aims to explore the development and treatment of these syndromes.

Introduction

Aging is a natural and dynamic process that takes place in living organisms as they develop over time, and it cannot be reversed. Aging is a common experience in the lives of humans, starting around the age of forty and continuing until death, which signifies the conclusion of biological life, as stated by most biologists. The aging process is intricate and unique to each individual, impacting the biological, psychological, and social aspects of life[1]. All physiological processes are affected by the natural process of aging. By the time individuals reach their thirties and forties, there are gradual and permanent shifts in the functioning of most organs, which continue to worsen as they age. The rate at which function deteriorates varies across different organ systems, but remains relatively stable within each specific system. Hence, the rate at which aging occurs is identical for a 45-year-old man and an 85-year-old man.[2, 3]

Normal age Changes

Some signs of aging can be seen from the outside: Your hair turns gray, and wrinkles and age spots appear on your skin. Our bodies are less able to store fluid in older age, so our spinal discs shrink and lose elasticity, for instance. Consequently, the aging process causes individuals to gradually decrease in height. It typically takes a while before changes in organs and tissues inside the body become noticeable. These characteristics may only be noticeable in certain individuals when they are under stress or in their later years. This occurs at an earlier time in different situations.

Cardiovascular Changes

Cardiac output decreases linearly after the third decade at a rate of about 1 percent per year in normal subjects otherwise free of cardiac disease. The cardiac index experiences a slightly slower decline, at a rate of 0.79 percent per year, due to the small decrease in surface area associated with aging [4]. Hypertension is commonly seen among individuals aged 65 and above, as it is often linked to the aging process. Vascular disease can also be caused by degenerative changes in blood vessels, such as lipid buildup, calcification, and changes in elasticity.[5]

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Respiratory System

While total lung capacity remains constant, the amount of residual volume increases as one gets older. Throughout adulthood, there is a decline of 20-30% in maximum voluntary ventilation, forced expiratory volume in one second, maximal expiratory flow rate, and maximum mid-expiratory flow. It has been noted that older patients are more susceptible to pulmonary infections such as pneumonia, possibly due to a weakened immune system and other factors.[6]

Urinary system

As people age, the size and weight of their kidneys gradually decrease, reaching about 70 percent of their original size by the age of 90. Additionally, the number of glomeruli per kidney decreases from approximately 1,000,000 below the age of 40 to around 700,000 by the time someone reaches 65 years old. As a result, elderly patients experience a decrease in creatinine clearance. Also, the half-life of a drug is influenced by age and carries clinical significance.[7]

Gastrointestinal System

The primary cause of age-related changes in oesophageal function, known as presbyesophagus, is disruptions in the motility of the esophagus. Older individuals may experience a reduced peristaltic response, an increased nonperistaltic response, slower passage of food, or decreased relaxation of the lower sphincter when swallowing. The slowing down of muscle contractions in the digestive system and the delay in the movement of food through the digestive tract can result in difficulty swallowing, leading to a voluntary reduction in calorie intake.[8]

The weight of the liver can decrease by up to 20 percent after the age of 50, but this decline may not be evident in the results of standard liver function tests, possibly due to the liver's significant reserve capacity. While liver function tests may not indicate significant changes with age, it is well-known that the elderly metabolize drugs like diazepam and antipyrine at a slower rate due to liver-related factors. The hepatic drug metabolism alteration might result from a decrease in the smooth endoplasmic reticulum's appearance, quantity, or distribution.[8]

Musculoskeletal System

The decline in lean body mass that occurs with age is widely recognized and is mainly caused by muscle cell loss and atrophy. Certain muscles, like the diaphragm, exhibit minimal to no alterations, whereas others, like the soleus, demonstrate significant infiltration of collagen and fat. More than 70% of individuals over the age of 70 experience degenerative joint disease, which is a leading cause of disability. Aging impacts both the peripheral and axial skeleton, causing cartilage degeneration, thickening of subchondral bone, eburnation, bone remodeling accompanied by the formation of marginal spurs and subarticular bone cysts.[9]

Causes of Aging

According to one prominent theory, our metabolism is responsible for the aging process. This theory suggests that aging is a result of regular metabolic processes. Approximately 2-3% of the oxygen atoms that enter the mitochondria are not adequately reduced and instead become reactive oxygen species (ROS). ROS, which are comprised of the superoxide ion, the hydroxyl radical, and hydrogen peroxide, are present in this context. Cell membranes, proteins, and nucleic acids can be damaged and oxidized by ROS [10]. The process of aging also involves another type of molecules called Reactive Nitrogen Species (RNS). All aerobic cells produce reactive oxygen and nitrogen species (RONS), which have a significant impact on aging and age-related diseases [11].

The "wear-and-tear" theories of aging have been around for a long time and are among the earliest explanations for the overall decline associated with aging. With increasing age, the body experiences a buildup of minor physical traumas. The number of point mutations rises, leading to a decrease in the efficiencies of the enzymes encoded by our genes. Additionally, in the event of a mutation in the protein synthesis machinery, a significant proportion of defective proteins would be produced by the cell. The occurrence of mutations in the enzymes responsible for DNA synthesis would result in a notable rise in the mutation rate. Murray and Holliday (1981) have extensively studied these defective DNA polymerases in cells that are aging.[12-14]

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Numerous genes have been demonstrated to impact the process of aging. Children with Hutchinson-Gilford progeria syndrome experience rapid aging and commonly pass away, usually from heart failure, before reaching the age of 12. A dominant mutant gene is responsible for this condition, which is characterized by thin skin with age spots, loss of bone mass, hair loss, and the development of arteriosclerosis. Mutations in the klotho gene in mice can also cause a comparable syndrome. The exact roles of these gene products are unknown, but they are believed to play a role in inhibiting the signs of aging. The significance of these proteins cannot be overstated regarding the timing of senescence.[10]

Different types of age Related Disease

Aging, both at the cellular and organismic level, is a intricate biological phenomenon that impacts every individual. With the increase in life expectancy, age-related illnesses pose a growing challenge for society and healthcare systems. Although it is an appealing idea, the development of a precise, molecular-based drug intervention for age-related diseases is currently not possible due to our limited knowledge of the molecular mechanisms that control the aging process.[15]

One possible approach to shed light on the molecular basis of aging processes is to study monogenic premature aging syndromes. Segmental progeroid syndromes (SPS) is the term used for a group of disorders characterized by signs of premature aging in more than one organ or tissue.[16]

Common indications of SPS consist of hair turning gray, cataracts, alterations in the skin, diabetes, osteoporosis, cancers, and cardiovascular issues, typically occurring in older individuals. Like regular human aging, the speed at which organs age differs, which is why it's called segmental syndrome. Growth retardation is another notable feature of SPS, as many of the genes associated with these syndromes are involved in different aspects of cell viability. Despite their rarity, with a global incidence estimated at around 1 in 50,000, SPS, which are typically hereditary, can serve as valuable research paradigms for understanding aging processes and age-related disorders. The scientific literature currently describes more than 100 syndromes characterized by clinical signs of premature aging. However, it is only in recent years that the genetic defects responsible for these syndromes have been discovered. These breakthroughs were achieved by analysing a small number of patients using high-throughput sequencing methods, commonly known as next-generation sequencing (NGS).[15]

This review will primarily focus on various diseases linked to premature aging. This review aims to give a comprehensive overview of the rapidly progressing field of identifying the causes of SPS, highlighting the significant advancements made in recent years. Furthermore, it will delve into the early achievements in developing a remedy for this ailment. This article will provide examples of SPS at different ages of onset, identified through a selective search of the PubMed database. Special clinical and genetic characteristics of these syndromes will be emphasized to help readers recognize these complex and diverse diseases at the earliest stage possible.

Wiedemann–Rautenstrauch Syndrome

Wiedemann-Rautenstrauch Syndrome (WRS) is a progeroid disorder where individuals experience a lack of subcutaneous fat and potentially other mesenchymal tissues[17]. The presence of multiple aging characteristics from birth has led to the designation of this condition as neonatal progeroid. The neonatal progeroid syndrome is a perplexing disorder, presenting a variety of symptoms that have yet to be fully understood in terms of their origin and progression. Rautenstrauch's 1977 report highlighted the cases of two sisters displaying progeria-like symptoms, which later became recognized as Wiedemann-Rautenstrauch syndrome (WRS)[18]. Autosomal recessive mutations in the POLR3A gene, which is found on chromosome 10q22.3, are linked to the disease[19]. The life expectancy of individuals with WRS is often shortened due to malnutrition-related conditions such as hypolipidemia and hypoalbuminemia, as well as complications following severe infections. The prognosis of WRS may be dependent on the presence and severity of mental and/or neurological impairment. The mental status in WRS patients ranges from normal to mild-to-moderate mental retardation but the latter is more common.[20]

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Clinical Signs and Diagnosis

Patients who are affected often display symptoms of premature aging such as pseudohydrocephalus, cranio-facial disproportion, decreased subcutaneous fat, thin skin, stiff and thick joints, and the presence of neonatal teeth. WRS is unique compared to other progerias due to the presence of all these changes from birth.[20]

PYCR1-related cutis laxa

Autosomal dominant cutis laxa (ADCL), a genetic disorder, is typically diagnosed in early childhood. The condition manifests as a less severe type of cutis laxa, frequently accompanied by systemic symptoms like hernias, cardiovascular complications, gastrointestinal diverticula, and emphysema. ADCL exhibits genetic heterogeneity, with documented mutations in the elastin gene (ELN). Mutations in PYCR1 have been detected in different types of cutis laxa syndrome, such as De Barsy syndrome and Wrinkly Skin syndrome, as well as in patients with ARCL2 who exhibit similar clinical symptoms to those with ATP6V0A2 deficiency. When exposed to oxidative stress, fibroblasts lacking PYCR1 displayed reduced mitochondrial membrane potential, disturbances in the mitochondrial network, and higher rates of apoptosis.[21]

Despite being located in the same pathway, defects in P5CS and PYCR1 have different impacts on patients. The presence of PYCR1 mutations results in less severe symptoms and a more positive prognosis, as it does not lead to neurological complications. The presence of a highly similar paralogue, PYCR2, can explain this phenomenon.

Clinical signs and diagnosis

The defining features of CL include excessive, sagging, non-elastic, and wrinkled skin. Inheritance of this skin and connective tissue disorder can occur through autosomal recessive, autosomal dominant, or X-linked recessive mechanisms, or it can be acquired. CL can present itself in various ways, including both generalized and localized manifestations, and there is a possibility of improvement over time in some patients. An abnormal histological staining and ultrastructure in a skin biopsy can provide further confirmation of defective elastin synthesis and structural abnormalities in extracellular matrix proteins, which are responsible for CL.[22]

Hutchinson-Gilford Progeria Syndrome

Hutchinson–Gilford progeria syndrome (HGPS) is an extremely rare genetic disorder characterized by accelerated aging, affecting approximately 1 in every 20 million births in the United States. In most cases, the LMNA gene is linked to de novo missense heterozygous mutations, resulting in the activation of a hidden splice site. As a result, the disease is not inherited by children from their parents.[23]

Despite being born seemingly healthy, these patients start showing symptoms within the first year of their lives, and the typical age for diagnosis is 2.9 years. The life expectancy of these children is just 13.4 years, and they commonly develop accelerated atherosclerosis, which usually leads to premature death caused by heart attacks or, less commonly, strokes.[24]

Clinical signs and Diagnosis

Severe growth failure, sclerodermatous skin, alopecia progressing to lipodystrophy, retrognathia, x-ray findings, delayed tooth eruption, and normal intellectual development may indicate Hutchinson-Gilford progeria syndrome (HGPS). HGPS is characterized by a disproportionately large head, a long narrow nose, thin lips, and retrognathia and micrognathia. Additional symptoms such as a thin, high-pitched voice and nocturnal lagophthalmos must also be considered for a proper diagnosis.[25]

Differential diagnosis

HGPS can be misdiagnosed as Wiedemann-Rautenstrauch syndrome or neonatal progeroid disorder, which are both autosomal recessive syndromes[23]. Mandibulo-acral dysplasia, Werner syndrome, Cockayne syndrome, and Hallerman-Strief syndrome are all part of the differential diagnosis for HGPS.[26]

Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome (MDPL) is a recently characterized rare condition, with an incidence of less than 1 in 1,000,000. Like individuals with HGPS, children who are affected appear normal when they are born. It is uncommon for the initial clinical symptoms to appear before the age of five. Progressive lipodystrophy, dental crowding, irregular tooth positioning, joint contractures, muscle wasting, hearing loss, and a high-pitched voice are observed starting

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from the age of 10. Later, patients frequently develop type 2 diabetes, telangiectasia, and osteopenia or osteoporosis. The oldest described patient was 62 years old at the time of the last follow-up examination.[27]

Werner syndrome

Clinical manifestations resembling accelerated aging are observed in individuals with WS, which is an uncommon genetic disorder. The initial description of WS was provided by Otto Werner, a German medical student, in 1904[28]. This condition is marked by an increased susceptibility to various age-related illnesses at an early age. Scientists achieved a major milestone in 1996 when they used positional cloning to discover the specific gene accountable for WS[29]. Individuals diagnosed with this disorder exhibit a higher inclination towards neoplastic growth. Thyroid follicular carcinomas are the most prevalent neoplasms in WS, followed by malignant melanoma, meningioma, soft tissue sarcomas, primary bone tumors, and leukemia/myelodysplasia. The increased risk of these neoplasms is between 2 to 60 times higher compared to the general population.

Clinical Findings and diagnosis

The first sign, sometimes only realized in hindsight, is a noticeable absence of a growth spurt and a final height that is relatively short for adults. In their early thirties, patients start to exhibit signs of aging, such as thinning skin, decreased fat under the skin, and the onset of grey hair. By the late 20s or early 30s, virtually all cases exhibit bilateral cataracts that necessitate surgery[30]. Included in these disorders are type 2 diabetes mellitus, hypogonadism, osteoporosis, atherosclerosis, and malignancies. According to various studies, it has been found that approximately 30-40% of individuals with WS had children prior to experiencing gonadal atrophy, which ultimately led to early infertility in their thirties.[31]

Therapeutic treatment

There is a vast potential for research and innovation within the field. Therapeutic drugs and targeted gene therapy are the two main methods of treatment. Significant progress has been made in the field of gene therapy technology. Nevertheless, there is still a lack of effective approaches for addressing age-related chronic diseases, which are frequently associated with genetic factors, including multiple genes. The journey towards developing cures is intricate, but targeting genes associated with aging through gene therapy presents a promising and captivating avenue for research.

Therapeutic drugs for age related disease

Metformin

For the last century, metformin has been a commonly prescribed medication for managing type 2 diabetes (T2D). Additionally, studies have demonstrated that metformin effectively decreases the development and death rates associated with cardiovascular diseases. Metformin has shown effectiveness in treating cancer, neurodegenerative diseases, and polycystic ovary syndrome.Metformin has beneficial effects on preventing and treating age-related illnesses as well. Following eight weeks of consistent metformin injections in SAMP8 mice, the levels of APPc99 and pTau in their brains were notably decreased, resulting in a significant improvement in the mice's learning and memory capabilities. It has been observed a useful drug to treat Alzheimer’s Disease (AD)[32]. Metformin focuses on the main aging pathways. Metformin reduces insulin levels and IGF-1 signaling outside cells, impacting various cytokines involved in anti-aging mechanisms. Metformin reduces ROS production within cells by inhibiting mitochondrial complex I in the electron transport chain and activating AMPK. Simultaneously inhibiting the mTOR signal and activating SIRT1 leads to a longer life-span. Aging is primarily linked to these cellular processes[33].

Side effects:. Drug prolong use or certain contraindicated conditions commonly lead to lactic acidosis. Possible side effects include hypoglycemia, vitamin B12 deficiency in T2D patients, diarrhea, vomiting, and GI problems.[34]

Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a phytoalexin found in many plant species, such as grapes, peanuts, and berries, which could respond to mechanical injury, fungal infection, and UV radiation. Resveratrol can enhance the growth of hUC-MSCs in a dose-dependent manner, delaying aging and activating SIRT1, while suppressing p53 and p16 expression. While resveratrol doesn't increase the lifespan of normal mammals, it can extend the lifespan of mammals with metabolic issues.

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In the fight against aging, resveratrol plays a role as an activator for sirtuins and the Nrf2 pathway. Resveratrol inhibits mitochondrial ATP production, activating AMPK and increasing NAD+ availability to boost SIRT1 enzyme activity. AMPK activity is positively controlled by the direct activation of SIRT1 by resveratrol. By interacting in a positive feedback loop, AMPK and SIRT1 collaborate to modulate several downstream factors and promote longevity. Moreover, resveratrol has the ability to directly interact with transcriptional regulators, exhibiting anti-inflammatory and antioxidant properties.[33]

Side effects. Diarrhoea and local allergies are potential serious side effects of resveratrol. The clinical application of resveratrol may be limited due to its low bioavailability. An additional hurdle is the limited feasibility of utilizing resveratrol in large-scale clinical trials currently.[35]

Rapamycin

Initially discovered as an antifungal agent, rapamycin is a macrolide produced by Streptomyces hygroscopicus. Rapamycin has been shown to extend the lifespan of yeast, C. elegans, and fruit flies by inhibiting the mTOR protein kinase, but its effects on mammals require further investigation. The main way rapamycin controls lifespan is by targeting the mTOR signaling pathway. mTOR can be found in two different complexes known as mTORC1 and mTORC2. mTORC1 is intermittently inhibited by rapamycin, while long-term use inhibits mTORC2 in most tissues. The inhibition of mTORC1 stimulates protein and nucleotide synthesis, triggers autophagy, and reduces cellular stress responses. The promotion of longevity could be a result of these rapamycin effects. On the other hand, when mTORC2 is inhibited, it causes metabolic dysfunction and a decrease in lifespan, although the specific mechanism is not yet understood.[33, 36]

Side Effects. The usage of rapamycin in high doses or over a long period of time can lead to stomatitis and mycositis, which involves ulceration of the mouth and digestive tract's mucous membranes. Rapamycin can cause a rare condition called noninfectious interstitial pneumonitis.[37]

Targeted Gene Therapy

As medical treatments often come with side effects, especially when they are long-term, it is crucial to develop alternative strategies. Alterations in a single gene or multiple genes are often the initial stages of aging-related diseases. Additionally, the effectiveness of medications often diminishes as conditions worsen, and higher doses intended to treat those worsening conditions come with inevitable side effects. In contrast, gene therapy offers a glimmer of hope for future cures of these diseases as it primarily targets the fundamental signs of aging. The term gene therapy, or genetic therapy, originally refers to techniques aimed at treating genetic disorders by introducing new DNA into specific cells or repairing the existing DNA.[38]

Nirenberg put forward genetic engineering applications in the 1960s, which had the potential to facilitate human gene therapy. Over the past few decades, significant progress has been made in gene therapy, with a particular focus on the revolutionary CRISPR technology. These technologies enable a wide range of modifications, including editing techniques like knockout, homologous recombination, and base editing, as well as epigenetic modifications that involve altering protein expression without changing the genetic information. Epigenetic modifications encompass a range of operations on genes, such as repression, activation, demethylation, and other similar processes. These techniques enable a more concise and precise regulation of gene expression.[39]

Gene replacement therapy

In gene therapy, gene replacement therapy now focuses on replacing a harmful gene with a functioning one or substituting a normal gene with an engineered version that has been strengthened to provide additional benefits. Viral vectors are commonly employed to mediate the transfer of exogenous cDNA in this strategy's delivery system[40]. Developed as a comprehensive anti-cancer treatment, Gendicine is the initial gene therapy drug that utilizes recombinant human p53 adenovirus[41].

The advancement of COVID-19 vaccines has led to the flourishing of functional RNA replacement, where lipid nanoparticles are primarily used to deliver therapeutic mRNA, making it a significant approach for gene therapy. A positive aspect is that the engineered mRNAs,

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when delivered, can be directly translated into functional therapeutic proteins that patients couldn't initially generate. However, engineered mRNAs have the potential to express exogenous tools like the CRISPR-Cas toolbox, which can be used for gene editing and modification. Advances in mRNA manufacturing and intracellular delivery methods have made it possible to clinically translate mRNA therapeutics[42].

This approach is ideal for addressing conditions caused by a single gene defect and is particularly effective in achieving localized effects without complex systemic interactions.

Gene Editing Therapy

Rather than overriding the expression of the disease-causing gene, an alternative approach is to modify local specific DNA sequences at the genomic level, which can lead to precise on-target mutations or small indels that effectively eliminate its effect. These changes consist of inserting a healthy or modified genetic sequence and making revisions, deletions, or substitutions to the sequence responsible for the disease. The initial goals for gene therapy are reflected in this strategy. Three highly effective tools for genome editing are TALEN, ZFN, and CRISPR. In the context of clinical and preclinical applications, only a few studies have been conducted and published that have cautiously examined gene editing without the use of auxiliary cellular products in living organisms[38]. These studies primarily focused on using vehicles and local administration to target and treat high-grade tumor tissues. In a recent study, Monian et al. introduced AIMers, a novel tool for efficient RNA base editing. These short chemically modified oligonucleotides can recruit endogenous ADAR, bypassing the need for exogenous enzymes and delivery vectors in adenine-to-inosine editing[43].

Epigenetic modification therapy

Other prospective approaches to treat diseases involve modification at the genetic level without changing the nucleic acid sequences. These approaches alter the expression of genetic information, such as inactivating a disease-causing gene, activating antagonist genes of the disease-causing genes, adjusting the imbalance in gene expression or correcting abnormal chemical modifications. The combination of Cas13-directed methyltransferase and TET3 fused with high-fidelity catalytically inactive Cas9 (dCas9) enables a broader range of precise epigenetic modifications compared to those achieved through regulatory noncoding RNAs such as short hairpin RNA (shRNA) and small interfering RNA (siRNA). As a result, the procedures for regulating epigenetics are increasingly moving towards standardization. Currently, this strategy is being developed and has primarily been tested for the treatment of cancerous tumors and in vivo CRISPR screening.[38, 44]

Conclusion

Age-related diseases may be uncommon, but they are challenging to treat and can also be emotionally draining. Having thorough research is crucial for the development of effective therapeutic treatments. Prolonged use of these medicines can result in serious side effects, so it is important to find a better alternative. Gene modification is a reliable and secure therapy that must be further developed in the future.

With advancements in aging research and improvements in sequencing technologies, more and more genes related to aging have been discovered. Extensive studies have been carried out to compare various tissues and cells in different stages and locations. It is possible that in the future, scientists will uncover millions of age-related genes that have both positive and negative associations with aging. Moreover, there have been reports of overlapping spectra between age-related diseases and aging-related genes in various studies. This suggests that there is significant potential in developing aging-related genes as targets for therapeutic interventions.

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