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Research Article

The Role of Klotho in Pediatric Premature Aging Diseases

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Abstract

The protein Klotho was first discovered in Klotho-deficient mice, which developed a syndrome similar to premature aging in humans. Since then, Klotho has been implicated in multiple molecular signalling pathways and diseases. Wnt activity and signalling pathways related to ageing and senescence: progerin, klotho and mTOR. Klotho has three different forms: soluble, membrane bounded and intracellular Klotho. All these three forms have different function. Klotho has been shown to have anti-aging, health span and lifespan extending, cognitive enhancing, anti-oxidative, anti-inflammatory, and anti-tumor properties. Two of three forms of Klotho protein, membrane Klotho and secreted Klotho, exert distinct functions. Membrane Klotho forms a complex with fibroblast growth factor receptors and functions as an obligate co-receptor for FGF23, a bone-derived hormone that induces phosphate excretion into urine. Mice lacking Klotho or FGF23 not only exhibit phosphate retention but also display a premature-aging syndrome, revealing an unexpected link between phosphate metabolism and aging. Secreted Klotho functions as a humoral factor that regulates activity of multiple glycoproteins on the cell surface, including ion channels and growth factor receptors such as insulin/insulin-like growth factor-1 receptors. Potential contribution of these multiple activities of Klotho protein to aging processes is discussed. Klotho levels decrease with age and in many diseases. It has been of great interest to develop a Klotho-boosting or restoring drug, or to supplement endogenous Klotho with exogenous Klotho genetic material or recombinant Klotho protein, and to use Klotho levels in the body as a biomarker for the efficacy of such drugs and for the diagnosis and management of paediatric diseases. First efforts were performed in mice and humans to add orally active and clinically translatable senolytics like Dasatinib or Quercetin to restore Klotho levels. Further research in this interesting field of Klotho interaction in growth and aging in children, especially in paediatric premature aging syndromes, is necessary. This is an overview of the role of Klotho in paediatric premature diseases.

Introduction

Aging is a general biological phenomenon that affects all human beings and results in a functional decline of physiological systems accompanied by an increased risk for chronic ailments with advancing chronological age [1-3]. At the molecular level, aging is associated with genomic instability, loss of heterochromatin, and the accumulation of macromolecular damage leading to reduced (stem) cell function and tissue regeneration. Progeroid disorders show many clinical features of aging-associated pathologies and signs similar to physiological aging; however, they occur at earlier ages and often progress rapidly. In many aspects progeria therefore represents a time-lapse form of aging. Premature aging processes are mostly segmental in that they involve one or more organs, but do not exhibit all aspects associated with physiological aging. Premature aging signs include, among others, alopecia, hair graying, lipodystrophy, osteoporosis, joint contractures, cataract, hearing loss, atherosclerosis, cardiovascular diseases, diabetes mellitus and malignancies at an early age. In addition to these typical aging phenotypes, progeria patients may also present with growth retardation, developmental delay, and intellectual disability. A more modular view of segmental premature aging syndromes hypothesizes that a cluster of symptoms appearing in several disorders might be due to a common underlying cause—for example, alopecia, osteoporosis, and nail atrophy have been proposed to be related to telomere shortening. Research into premature aging disorders

aims at understanding the pathogenesis and to develop novel treatment strategies, but also intends to unshadow physiological aging processes since premature aging phenotypes mirror many of the clinical aspects of physiological aging. One of the best-known premature aging disorders is the Hutchinson-Gilford Progeria Syndrome (HGPS), for which the molecular pathogenesis is largely uncovered, and additionally promising treatment approaches have been tested in first clinical studies. Moreover, more than 100 additional premature aging phenotypes have been described with an overall global incidence of approximately 1:50 000 [1,4,5]. Syndromes associated with premature ageing comprise a clinically and genetically heterogeneous group of disorders [1-72]. Werner syndrome and Bloom syndrome both arise due to DNA helicase gene mutations resulting in growth deficiency and a predisposition to malignancy, amongst other features [38-44]. Another mechanism of premature ageing arises in the progeroid laminopathies whereby aberrant lamin A processing leads to the accumulation of progerin in the cell nucleus, variably causing severe growth retardation, accelerated ageing, skeletal abnormalities and early death from cardiovascular disease [6,1,2,17-19,22,62-72].

The cutis laxa syndromes result from mutations in genes involved in the formation or modification of elastic fibres, giving rise clinically to lax skin in addition to gastrointestinal, genito-urinary, vascular or pulmonary compromise. The association of premature ageing syndromes with significant and severe systemic features highlights the need for accurate clinical and molecular characterization of affected individuals. Nine molecular and cellular hallmarks have been proposed to drive the main mechanisms of physiological and pathological aging: genomic instability, telomere attribution, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, deregulated nutrient sensing, stem cell exhaustion, cellular senescence and altered intercellular communication. These hallmarks represent no independent mechanisms; rather, they are intertwined and influence each other, contributing in a specific manner to the complex pathogenesis of different aging-associated disorders. Impairments of several physiological systems are also involved in premature aging. Alterations in nuclear lamina proteins leading to the disruption of the nuclear envelope and to nuclear blebbing are more related to HGPS, Nestor-Guillermo progeria syndrome, congenital restrictive dermopathy, and mandibuloacral dysplasia. Defects in DNA repair causing genomic instability and increased cancer risk are associated with RecQ helicase-mutant disorders such as Werner syndrome and Bloom syndrome [38-44, 51-59], but play also a role in Ataxia-telangiectasia, Cockayne syndrome [45-50], Nijmegen breakage syndrome [73-75], Seckel syndrome [76] and xeroderma pigmentosum, among others. Major effects of telomere attrition are for example known for dyskeratosis congenital and Hoyeraal-Hreidarsson syndrome [77-81], although telomere dysfunction has been described in almost all premature aging syndromes associated with genomic instability. Likewise, mitochondrial dysfunction is frequently observed. It is a key characteristic of Fontaine progeroid syndrome [82-86] and some progeroid cutis laxa syndromes, but also contributes to the pathogenesis of several other progeroid disorders such as HGPS, mandibuloacral dysplasia type B, Cockayne syndrome [45-50], ataxia-telangiectasia, and xeroderma pigmentosum.

Pediatric Pre-Aging Diseases

Progeroid Laminopathies

Hutchinson-Gilford-Progeria (Joseph Syndrome, progeria syndrome): HGPS is an early-onset premature aging disorder that occurs approximately in 1:4 to 8 million live births and has been reported in more than 250 cases worldwide [6,1,2,17-19,22,62-72]. The prevalence is estimated at 1:4,000,000-1:8000000. Patients die at a mean age of 12.6 years mostly due to progressive atherosclerosis and cardiovascular diseases [6,1,2,17-19,22,62-72]. It belongs to the segmental progeroid syndromes (SPS; rare diseases with signs of premature aging in more than one organ or tissue) or progeria syndromes and is a clinical sign of various hereditary diseases associated with rapid aging in children [6,1,2,17-19,22,62-72]. The Hutchinson-Gilford syndrome is an autosomal-dominant disease of various tissues that leads to a massive and very early onset of aging of the skin, skeleton and blood vessels in early childhood [62-72]. Some authors also suggest an autosomal recessive mode of inheritance. The autosomal-dominant inherited Hutchinson-Gilford syndrome is caused by a defect of the LMNA gene on one allele of chromosome 1 (1q21.3), which is responsible for the protein lamin A/C. Lamin A/C is a protein found in the nuclear membrane of most cells that functions as a filament system attachment point and presumably also as a regulator of gene transcription. In a majority of patients with Hutchinson-Gilford syndrome, codon 608 is altered, resulting in a cryptic splice site is activated. This results in the loss of 150 nucleotides of the exon 11 are lost, resulting in the loss of 50 internal amino acids in the later protein, the progerin called progerin. In addition to Hutchinson-Gilford syndrome, mutations in the LMNA gene can also cause other diseases. Hutchinson-Gilford progeria syndrome is typically caused by a dominant-negative C•G-to-T•A mutation (c.1824 C>T; p.G608G) in LMNA, the gene that encodes nuclear lamin A. This mutation causes RNA mis-splicing that produces progerin, a toxic protein that induces rapid ageing and shortens the lifespan of children with progeria to approximately 14 years [22]. Differential diagnosis includes Hallermann-Streiff syndrome, Gottron syndrome and Wiedemann-Rautenstrauch syndrome [31-37]. The usual onset is 9-24 months . However, the reason for the differences in the respective clinical pictures is not yet understood. The clinical picture was first described by Jonathan Hutchinson and Hastings Gilford in 1886. The most striking feature is a premature senescence of the affected children. Those affected age five to ten times faster than people without this disease. The most frequent causes of death are heart attacks and strokes, which already occur in childhood or adolescence. However, many phenomena of normal aging do not occur in children with HGPS; for example, the risk of tumors is not relevantly increased, and neurodegenerative diseases such as Alzheimer's disease do not occur

more frequently. HGPS is thus not an exact copy of normal aging. Life expectancy is fourteen years [6,1,2,17-19,22,62-72].

Since the molecular mechanisms of regulation of aging processes are incompletely known, there is no possibility of prevention or therapy by drug manipulation of currently studied molecular processes in age-associated diseases such as segmental progeroid syndromes. One cause of progeria, congenital restrictive dermopathy, is also a point mutation c.794 A→G (N265S) (chromosome 1 gene locus p34.2) in the ZMPSTE24 gene, which encodes the enzyme CAAX-prenyl protease or zinc metallopeptidase-Ste-24 homolog. This is essential for the formation of the structural protein lamin A, which is an important component of the inner nuclear membrane. Mutant ZMPSTE24 cannot necessarily separate prelamin A at amino acid 647 to eliminate prenylation and produce the finished 646 AA (amino acid)-long lamin A. However, in the majority of cases of HGPS, a mutation of the prelamin gene in codon 608 on chromosome 1 gene locus q23 itself occurs, changing the trinucleotide GGC to GGT. Although this codes for the same amino acid (Gly), the altered base sequence inserts a splice site (5'AC) in the corresponding pre-mRNA. This faulty splicing results in a prelamin RNA that is 150 bases shorter and a lamin A that is 50 AA shorter, also known as progerin. The interface for processing to lamin A is missing, and ZMPSTE24 is unable to cut prelamin A. A too short prenylated lamin remains. Less commonly, a change in codon 608 in AGT or a mutation in codon 145 is found. Lamin A (structural protein of the nuclear membrane encoded by the twelve-exon gene LMNA) is part of a protein chain that binds to numerous other proteins of the nucleus and nuclear membrane, as well as to transcription factors and DNA. It performs a stabilizing function of the cell nucleus as well as regulatory functions. Among other things, it participates in the activation of genes. New gene therapy efforts were performed successfully recently in mice [62,65,66,70].

Nestor-Guillermo Progeria Syndrome: Nestor-Guillermo progeria syndrome has so far been described only in two unrelated patients [3,26-30]. This rare disorder was discovered when 2 seemingly healthy twin boys named Nestor and Guillermo were born in Spain, starting at the age of 2, they rapidly started aging, when they were 10 years old, they had loose hair and their skin started wrinkling, their bones started weaking and their stature barely increased, it was clear they had progeria; however, their doctors couldn't find what type of progeria they had, since they didn't present cardiovascular abnormalities and they didn't have the known genetic mutations of the mentioned progeroid syndromes, that's when their shared genetic mutations (BANF1) were discovered, and with that discovery came the revelation of a novel progeroid syndrome, by 2011, they were already 20-30 years old [3,26-30]. The disease is autosomal-recessive and found with an incidence of 1:1000000 [3,26-30]. It shares phenotypic features with HGPS including facial progeroid appearance, growth retardation, generalized lipodystrophy, and joint contractures [3,26-30]. However, both patients do not suffer from cognitive involvement, atherosclerosis or metabolic complications until their early adulthood and show a slow clinical course and a relatively long lifespan. Characteristically, they exhibit severe osteoporosis and marked osteolysis [3,26-30]. Exome sequencing identified in both patients a homozygous point mutation (c.34G>A; p.Ala12Thr) in BANF1, which encodes the BAF protein [3,26-30]. The mutation reduces the ability of BAF to bind DNA, leading to the disruption of the nuclear envelope, which contributes to the cellular phenotype of Nestor-Guillermo progeria syndrome [3,26-30].

Klotho Deficiency: Klotho deficiency causes cardiac aging via impairing the Nrf2-GR pathway [7,9,23]. Supplement of exogenous secreted Klotho represents a promising therapeutic strategy for aging-associated cardiomyopathy and heart failure [7]. Klotho deficiency is related to aging-associated salt-sensitive hypertension due to vascular Wnt5a/RhoA activation [8]. Klotho deficiency-induced arterial calcification is a process that includes the osteoblastic transition of SMCs and activation of BMP2-RUNX2 signalling [9]. Treatment with recombinant Klotho protein abolished BMP2/vitamin D3-induced osteoblastic transition and morphogenesis and calcification. Therefore, Klotho is a critical regulator in the maintenance of normal arterial homeostasis [9]. It seems to be evidence suggested that Klotho is an independent contributing factor for uremic cardiomyopathy and a possible new target for treatment of this disease [10]. In one study, induced miR-34a overexpression promoted epithelial-to-mesenchymal transition (EMT) in cultured human renal tubular epithelial HK-2 cells, which was accompanied by sharp downregulation of Klotho, an endogenous inhibitor of renal fibrosis; therefore, Klotho deficiency could induce renal fibrosis [5]. Genetic klotho deficiency decreased lifespan and cardiac function in mice, impaired autophagic activity and increased apoptotic activity [4]. Exogenous klotho attenuated cardiomyocyte ageing and reversed changes in autophagic and apoptotic activity caused by D-gal. Moreover, klotho supplementation prevented D-gal-induced oxidative stress and cytotoxicity [4]. Arteriolar hyalinosis is caused In Klotho deficiency, a state known to induce both renal and vascular phenotypes associated with aging [13]. In one important study, genetic background was a key but sometimes overlooked factor that profoundly impacts disease susceptibility and presentation in both humans and disease models [14]. Deficiency of Klotho protein causes different phenotypes in 129S1/SvlmJ (129) and C57BL/6J (B6) mouse strains [14]. The 129 strain is more severely affected, with decreased longevity, decreased body weight, and increased amounts of kidney calcification compared with B6 mice [14]. Reciprocal F1 crosses of the strains also indicate a parentage effect on the Klotho phenotype with F1 Klotho-deficient progeny of B6 mothers and 129 fathers having more kidney calcification than progeny of 129 mothers and B6 fathers. Comparing and contrasting the genetic architecture leading to different phenotypes associated with specific inbred mouse strains may reveal previously unrecognized and important metabolic interactions affecting chronic kidney disease [14]. Klotho levels were significantly lower among children with organic GHD compared to both GH sufficient participants and those with idiopathic GHD. The difference between GHS chil-

dren and children with idiopathic GHD was not significant. Klotho levels positively correlated with IGF-1- standard deviation scores (SDS), but were not associated with gender, pubertal status, age or anthropometric measurements [23].

Werner Syndrome (Rabbiosi Syndrome): Werner syndrome, named after the German physician Otto Werner (1879-1936), is an autosomal recessive disorder, primarily of mesodermal tissues, that leads to premature aging (progeria) beginning around midlife. It is a juvenile segmental progeroid syndrome and is one of the chromosome break syndromes [51-59]. Synonyms are progeria adultorum, Rabbiosi syndrome and English adult progeria. In autosomal recessive Werner syndrome, there is a defect in the WRN gene (also called RecQL2) on the short arm of chromosome 8 (p12-p11.2), which codes for a RecQ family DNA helicase [51-59]. These proteins are involved in repairing damage to the genetic material. The defect at the WRN gene leads to an increased mutation rate, especially DNA deletions, and a rapid shortening of telomeres. In general, the increase of errors in DNA replication is assumed. Werner syndrome is a very rare disease. It occurs more frequently in Japan. The literature gives a frequency of about 3:1,000,000 for there [51-59]. The risk of developing the disease seems to be increased-as is typical for autosomal recessive diseases-in children from consanguineous marriages. Until puberty, affected individuals develop normally. The symptoms of this juvenile segmental progeroid syndrome begin at about puberty in patients with Werner syndrome, the first signs being reduced longitudinal growth and a weak and high-pitched voice [51-59]. The full-blown disease usually manifests itself after the age of 30. Patients appear old in early adulthood, showing thin, translucent skin (dystrophy) that calcifies with age; there is loss of subcutaneous fat and pigmentation. In addition, typical signs of aging are whitish, sparse hair, cataract, diabetes mellitus type II, arteriosclerosis, muscle loss and osteoporosis. Due to the high mutation rate, malignant tumors (in contrast to tumors of normal aging, mainly sarcomas) are frequently described in patients with Werner syndrome, which are usually life-limiting in addition to complications of arteriosclerotic changes like myocardial infarction and apoplexy [51-59]. Most patients die before the age of 50 [51-59]. The Flynn-Aird syndrome or CARASIL, among others, should be distinguished [60, 61]. Causal therapy is not available to date. Treatment is limited to prophylaxis and therapy of complications.

Bloom Syndrome (BSyn): The overall prevalence of Bloom syndrome (BSyn) is not known, but in the Ashkenazi Jewish population it is estimated to be about 1 in 48,000 births (38-44). Endermutation, known as BLMash, is present in about 1 in 100 persons of Ashkenazi origin. Founder mutations are also present in the Slavic and Hispanic populations. Individuals with BSyn exhibit a proportional growth deficiency that begins prenatally (average birth weight 1757 g) and persists throughout life (average adult height of 149 cm for males and 138 cm for females). Observed features include dolichocephaly, a narrow face, prominent nose and protruding ears, and malar and mandibular hypoplasia [38-44]. There is little subcutaneous adipose tissue. Telangiectatic erythema occurs on the face, especially on the cheeks, dorsum of the hands, and other sun-exposed areas during the first 1-2 years of life. Café-au-lait spots and hypopigmented skin lesions are common. Children with BSyn are characterized by slow food intake, decreased appetite, and eating a limited variety of foods. Despite nutritional interventions, weight gain is modest, and children are rarely within the normal growth range. A major feature of Bsyn is a greatly increased predisposition to cancer, with a distribution similar to that of the general population but occurring at a much younger age. Survivors of a first cancer may have multiple cancers during their lifetime [38-44]. Most men with BSyn have azoospermia or severe oligospermia, while women do not have impaired fertility but may experience premature menopause [38-44]. Bsyn is due to mutations in the BLM gene (15q26.1), which encodes the DNA helicase RecQl3 [38-44]. This is an enzyme involved in maintaining genomic integrity. The mutations result in a spontaneously increased proportion of sister chromatid exchanges due to a slowdown in replication speed and defective fork reactivation.

Congenital Restrictive Dermopathy: Congenital Restrictive dermopathy is a severe congenital genodermatosis, a form of arthrogryposis multiplex, with approximately 80 cases reported worldwide, which is lethal mostly within the first weeks of life [87-92]. Main clinical features are thin, tightly adherent translucent skin with erosions at flexure sites, prominent vessels, characteristic facial dysmorphism, generalized joint contractures, dysplasia of clavicles, and respiratory insufficiency [87-92]. Prenatally, intrauterine growth retardation, fetal hypokinesia, and polyhydramnios can be observed. In most cases, compound heterozygous or homozygous null mutations in the ZMPSTE24 gene are causative of restrictive dermopathy. Less frequently, autosomal dominant mutations in the LMNA gene are causative of restrictive dermopathy, leading to a truncated prelamin A protein, which cannot undergo full posttranslational maturation and accumulates inside the nucleus. Mutations in both genes, thereby, induce nuclear structural and functional alterations [87-92].

Cutis Laxa Syndrome: Cutis laxa (Latin for "flabby skin") is a hereditary congenital or acquired disease of the connective tissue with wrinkled, sagging and flabby inelastic skin [93-95]. The term "dermatochalasis" is used for the diagnosis and differential diagnosis of the disease. At this point, only the syndromes are listed as congenital forms, all others including diagnostics and differential diagnosis can be found under the conceptual synonym dermatochalasis. The incidence is reported to be about 1 in 1,000,000, and about 200 patients have been described to date [93-95]. The etiology of the hereditary forms is apparently very heterogeneous; a number of involved genes have been identified in affected individuals to date. Currently, the following forms are distinguished according to the mode of inheritance and clinical presentation. The forms with autosomal recessive inheritance (ARCL) are further subdivided into: ARCL1 (Cutis laxa, autosomal recessive, type 1) as the most severe form with life-threatening complications [93-95]. According to the localization of the mutations found so far, there

is a further subdivision into: ARCL1A with mutations at the FBLN5 gene at location 14q32.12, ARCL1B with mutations at the EFEMP2 gene at location 11q13.1, ARCL1C cutis laxa with severe associated lung, gastrointestinal, and urinary tract abnormalities or Urban-Rifkin-Davis syndrome with mutations at the LTBP4 gene at location 19q13.2, ARCL2 (cutis laxa, autosomal recessive, type 2) with a combination of cutis laxa, joint instability, and developmental delay. These are diseases with a wide range of clinical abnormalities, including some overlap in the genetic alterations found. PYCR1-associated cutis laxa is one of the congenital segmental progeroid syndromes (rare inherited disorders in which signs of premature aging-cf. also progeria-are seen in more than one organ or tissue. Wrinkly skin syndrome with wrinkly skin disease with mutations in the ATP6V0A2 gene at location 12q24.31 [96]. Classic form type Debré with more severe changes, growth retardation and skeletal abnormalities. Here, mutations were found at the ATP6V0A2 and PYCR1 genes at location 12q24.3 and 17q25.3, respectively. ARCL2A Cutis laxa, autosomal recessive, type 2A. ARCL2B Cutis laxa, autosomal recessive, type 2B or progeroid form with mutations at the PYCR1 gene at location 17q25.3. ARCL3A or De-Barsy syndrome A (cutis laxa-corneal opacity-mental retardation). ARCL3B or De-Barsy syndrome B (Cutis laxa, autosomal recessive, type IIIB) with mutations on the PYCR1 gene at location 17q25.3 [93-95].

Hallermann-Streiff-Syndrome: Hallermann-Streiff syndrome (HSS for short, other names: Bird's disease, Hallermann-Streiff-François syndrome, English: Oculomandibulodyscephaly with hypotrichosis, Oculomandibulofacial syndrome) is a rare, sporadically occurring malformation syndrome in humans [31-37]. Only about one hundred cases have been described in the literature [31-37]. However, there are reports of familial frequency. Affected individuals exhibit, among other features, proportionate short stature, a peculiar facial shape with a very small, beak-like curved nose and small lower jaw (micrognathia), congenital eye malformation with an eyeball that is too small (microphthalmia) and opacification of the lenses (congenital cataract), and thinning hair [31-37]. The tongue of people with HSS usually develops to a usual size, so that it is disproportionately large in relation to the small body [31-37]. This often leads to problems with eating and breathing. Due to the malformed eyes, severe visual impairment or even blindness usually occurs. Cognitive disability may accompany HSS. The genetic cause of HSS is not known. Due to the rarity of HSS, scientific studies on this topic mostly consist of comparisons of individual cases. Affected individuals often also have Worm's bones. The disease was named after two ophthalmologists, Wilhelm Hallermann (1909-2005) and Enrico Bernardo Streiff (1908-1988) [31-37]. Hallermann-Streiff Syndrome and lower limb lymphedema with nasal obstruction has been described recently [35].

Cockayne Syndrome: Cockayne syndrome is a rare developmental and neurodegenerative disorder with more than 120 genetically confirmed patients worldwide [45-50]. The annual incidence is estimated at approximately 1:250 000 and the prevalence at approximately 2.5 per million [45-50]. The typical phenotype is characterized by cachectic dwarfism with sunken eyes and progressive microcephaly with structural brain anomalies, severe developmental delay and mental retardation. The clinical spectrum also includes cutaneous photosensitivity, pigmentary retinopathy, cataracts, sensorineural hearing loss, atherosclerosis, feeding difficulties, and dental anomalies. Most patients die from progressive multiorgan degeneration in the first or second decade with a mean age of death of 12 years [45-50]. Two genes have been identified to be mainly associated with the disease in an autosomal recessive inheritance pattern: Cockayne syndrome type A is linked to mutations in ERCC8 (one-third of the patients) and Cockayne syndrome type B to mutations in ERCC6 (two-thirds of the patients) [45-50]. The majority of the mutations are truncating, but missense substitutions are also reported. Both genes encode components involved in the NER of UV-induced and oxidative DNA damage and play a role in mitochondrial DNA metabolism and neuronal differentiation [45-50]. Pathogenic mutations in ERCC6 are also known to cause cerebrooculofacioskeletal syndrome, De Sanctis-Cacchione syndrome, UV-sensitive syndrome and premature ovarian failure [45-50] (Table 1).

Table 1: Overview of different paediatric premature aging syndromes.

Most Important Premature Aging Syndromes				
Pathogenesis of Premature Aging	Case Parameters	Role of Klotho	Therapy	
Hutchinson-Gilford Syndrome ([6,1,2,17-19,22,62-72]	Progeroid Laminopathy: dominant-negative C•G-to-T•A mutation (c.1824 C>T; p.G608G) in LMNA ([6,1,2,17-19,22,62-72]	200-250 cases to date; Alpha Klotho was identified as „progeria-causing protein" [98,99]. The hypothesis that disruption of the klotho–FGF-23 axis is one potentially treatable downstream consequence of the expression of progerin should be further evaluated [6]. Death within average 12.6 years.		Application of gene therapy based Crisp/Cas technology [70] In vivo base editing in „mice"[62]

Nestor-Guillermo Progeria Syndrome [3,26-30]	Progeroid Laminopathy: homozygous point mutation (c.34G>A; p.Ala12Thr) in BANF1 [3,26-30], chromosome 11q13.1 A12T founder mutation.	Autosomal- recessive inheritance, incidence 1:1000000; 4 variants; Onset after 2 y of age, alive a long lifespan, search in progeria patient, when LMNA/ ZMPSTE24 mutation negative.	No study found towards Klotho blood and urine levels in this disease	No therapy
Klotho Deficiency	Low levels of Klotho		Impaired Nrf2-GR and Wnt-Pathway	First efforts were performed in mice and humans to treat patients with idiopathic pulmonary fibrosis with orally active clinically translatable senolytics, Dasatinib and Quercetin, to restore alpha Klotho levels published in Lancet 2022 [97].
Cutis Laxa Syndrome [94-96]	ARCL-Mutations [94-96]	200 cases to date	No study found towards Klotho blood and urine levels	There is no specific treatment for cutis laxa. Physical therapy can sometimes help increase skin tone. Plastic surgery can dramatically improve the appearance of patients with inherited cutis laxa, but it is less successful for the acquired form
RecQ-helicase-mutant disorder: Werner Syndrome [51-59]	Chromosome Break Syndrome: Defect in the WRN gene on short arm of chromosome 8 (p12-p11.2), which codes for a RecQ family DNA helicase [51-59, 97]	full expression after age 30; death before age 50	No study found towards Klotho blood and urine levels	Depending upon such factors, treatment methods may include Genetic counseling is recommended for individuals with Werner syndrome and their families.
RecQ-helicase-mutant disorder: Bloom Syndrome [38-44]	Mutations in the BLM gene (15q26.1), which encodes the DNA helicase Rec Ql3 [38-44,97]	Autosomal recessive inheritance Incidence 1:48000 (jewish newborn); Death: Average 30y	No study found towards Klotho blood and urine levels	Treatment is symptomatic. Higher caloric density in the form of special formulas and foods can promote weight gain and growth. Although growth hormone treatment can improve length growth, many physicians advise against its use because early onset of cancer has been observed in some treated children. Standard antibiotic regimens are used to treat infections. For low serum levels of immunoglobulins and repeated infections, treatment with intravenous or subcutaneous immunoglobulins was given to some patients. Skin protection, including covering exposed skin and using a broad-spectrum sunscreen with a SPF of at least 30, is critical to reduce sun-sensitive rash. Recommendations for medical surveillance of individuals with Bloom syndrome have been published, including recommendations for cancer screening. Due to patient hypersensitivity to chemotherapy, reduced dosage and/or duration of therapy is recommended, usually starting at 50% of the weight-based dosage.
Congenital Restrictive Dermopathy [73-80]	Mutations in the ZMPSTE24 gene [73-80]	80 cases to date, form of congenital lethal arthrogryposis multiplex [73-80]	No study found towards Klotho blood and urine levels	No therapy

Hallermann-Streiff Syndrome [31-37]	Genetic Cause unknown, sporadic [31-37]	150 cases to date , first record of this disorder was made by Aubry in 1893. More than 150 cases of HSS have been reported till date [31-37]; Association with Lower Limb Lymphedema and Nasal Obstruction [35]	No study found towards Klotho blood and urine levels	No therapy
RecQ-helicase-mutant disorder: Cockayne-Syndrome [45-50]	Cockayne syndrome type A is linked to mutations in ERCC8; Cockayne syndrome type B to mutations in ERCC6 [45-50]	120 cases to date; association with UV sensitivity, hepatotoxicity of metronidazole, pseudopapilledema [45-50]	No study found towards Klotho blood and urine levels	No therapy

Discussion

Premature pediatric aging syndromes are very rare diseases worldwide. Hutchinson-Gilford progeria was described in around 250 children worldwide. Most often, sporadic forms, mutations or chromosomal breaks play the major role in pathogenesis of the diseases. Curing these extremely rare diseases make gene therapy efforts unwillingly necessary. First efforts were performed to cure Hutchinson-Gilford syndrome based on CRISP/CAS 9 technology [62,70]. This was performed in mice model successfully by *Koblan, et al.,* published in Nature 2021 [62].

Concerning the role of klotho, it is a proteohormone that can prolong life in mice by approximately 20 to 30% [97-100]. It is a membrane-bound protein with a size of 130 kDa. In addition, there is a soluble form of the protein called solube Klotho (sKL). Proteolytic cleavage upstream (α-cut) or downstream (β-cut) of the KL2 domain of the protein, results in either a 130-kDa sKL, or 60-70-kDa klotho fragments. In 1997, Makoto Kuro'o at the National Institute of Neuroscience in Tokyo identified a new gene that extends lifespan in mice when expressed in increased amounts. A defect in this gene leads to a syndrome similar to human aging. Affected animals have a reduced life expectancy, are infertile and develop typical age-related diseases such as arteriosclerosis, skin atrophy, osteoporosis and emphysema. The Klotho gene encodes a transmembrane protein with a transmembrane domain. The Klotho protein binds as a co-receptor to several fibroblast growth factor receptors. The secreted Klotho protein regulates several signaling pathways, including the insulin/IGF-1 pathway and the Wnt signaling pathway, as well as the activity of many ion channels. In addition, Klotho protein protects cells and tissues from oxidative stress. Alpha Klotho plays an important role and was identified as „progeria-causing protein"[79,80]. In this relation, hypothesis that disruption of the Klotho-FGF-23 axis is one potentially treatable downstream consequence of the expression of progerin should be further evaluated [6].

First efforts were performed in mice and humans to treat patients with idiopathic pulmonary fibrosis with orally active clinically translatable senolytics, Dasatinib and Quercetin, to restore alpha Klotho levels published in Lancet 2022 [97-100]. In paediatric premature aging syndromes this was never measured nor performed. It would be very interesting to measure Klotho levels in blood and urine in early diagnosed paediatric premature aging diseases, especially in Hutchinson-Gilford progeria paediatric patients to concrete the exact role of Klotho in aging of these children. Moreover, it could be therapeutical important to know, if any additional exogenous Klotho application could ameliorate the course of disease in the population of paediatric premature aging. Studies towards this aspect are still missing due to the low number of populations acquainted with this rare pre-aging diseases in childhood. Further intensive research in this field is necessary.

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Conflict of Interest

None.

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