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Part One

Introduction

Hutchinson-Gilford progeria syndrome (HGPS) (Progeria)(MIM176670), is a rare fatal genetic disorder characterized by premature aging.\textsuperscript{1} It was first described in late 19th-century England by Drs. Jonathan Hutchinson and Hastings Gilford.\textsuperscript{2,3} Progeria is derived from the Greek words \textit{pro} (προ) and \textit{geras} (γῆρας), meaning premature aging. HGPS is characterized by premature, accelerated aging with onset in early childhood.

Epidemiology

HGPS is considered an orphan disease with sporadic, autosomal dominant transition and without gender or ethnic propensity.\textsuperscript{4,5,6,7} The incidence of Progeria is estimated at 1 in 4 million, with an estimated prevalence of 350 children worldwide. As of December 2016, the Progeria Research Foundation International Registry has identified 140 children.\textsuperscript{8} HGPS is an autosomal dominant disease with complete penetrance as a result of a de novo mutation in the \textit{LMNA} gene,\textsuperscript{4,5} however because of a single case of somatic and gonadal mosaicism\textsuperscript{3} the recurrence risk for a future sibling to a child with Progeria is estimated to be one in 500.\textsuperscript{1} Children affected by Progeria die from cardiovascular disease, mean survival was at a mean age of 14.6, ranging from 1.6 to 27.5 years.\textsuperscript{10} Ophthalmic manifestations of Progeria include cornea dryness and keratopathy, in addition children with Progeria have been noted to be hyperopic.\textsuperscript{11} However due to the rare nature of the disease an accurate incidence of ophthalmic manifestations is not available.
Molecular pathogenesis

Approximately 100 years after HGPS was first described the gene responsible for the disease was identified in 2003, a single de novo nucleotide substitution at position 1824 (C→T) in the LMNA gene is the most common cause of Progeria.45

LMNA Gene

The LMNA gene is located in the long arm of chromosome 1, region 2, band 1, sub-band 2 (1q21.2).1213 It spans 57.6 kb of DNA and consists of 12 exons, which through alternate splicing encodes for four proteins, two major: lamin A and lamin C; and two minor: lamin AΔ10 and lamin C2.141516

Lamins are intermediate filaments and are part of the nuclear lamina. The nuclear lamina is the innermost layer of the nuclear envelope and consists of a thin (20-50nm) protein meshwork. It plays an important role in the structural integrity of the nucleus and separates the nucleus from the cytoplasm.1718 Lamin A is responsible for key nuclear functions, including nuclear structure, chromatin organization and function, gene transcription via DNA replication and RNA transcription, and regulation of the cell cycle.

The mature lamin A protein is a product of further processing of its precursor, prelamin A. Prelamin A requires transcription from DNA to messenger RNA of all 12 exons of the LMNA gene. Prelamin A undergoes four stages of processing to become lamin A, this includes farnesylation, cleavage of the last three amino acids of the carboxy terminal, methyl esterification and proteolysis of the 18 amino acids of the carboxy terminal.192021 Farnesylation is a critical part of the process for incorporation of prelamin A to the inner nuclear membrane. The post translational proteolysis of the 18 amino acids from the C-
terminus of the prelamin A protein includes the farnesyl group that had been added. Loss of the farnesyl group results in release of prelamin from the inner nuclear membrane with subsequent degradation. 20

Lamin A has tissue and cell specificity, its function is upregulated in fibroblasts, vascular smooth muscle cells and vascular endothelial cells. 16 22 23

Progerin

In HGPS the most common mutation in the LMNA gene is the result of a single-base substitution from cytosine to thymine GGC>GGT in codon 608. A less frequent single-base substitution in the same codon from cytosine to adenine GGC>GGA has been predicted to have the same effect on lamin A. The mutation reveals an alternate pre-mRNA splice site in exon 11 that results in a 50-amino acid deletion in the translated lamin A. 4 5 This truncated mutant lamin A protein is referred to as progerin. Progerin lacks the endoproteolytic cleavage site targeted by the ZMPSTE21 endoprotease that normally results in proteolysis of the C-terminus amino acids, including the farnesylated cysteine. 13 20 21 Thus, progerin retains the farnesylated cysteine at the C-terminus, which leads to incorporation of the mutant protein to the inner nuclear membrane with subsequent disruption of its structural integrity. This occurs in a dominant negative fashion (Figure 1). 4 5
Figure 1. The LMNA mutation and lamin A processing in HGPS.
In HGPS, the single point mutation of a C to T at position 1824 of codon 608 does not change the encoded amino acid, glycine. However, it does activate a cryptic splice site 150 nucleotides upstream of the usual exon 11 to 12 splice junction. The lamin A precursor, prelamin A, undergoes a series of posttranslational modifications, including farnesylation at its C-terminal CAAX motif (CSIM in this case) by the enzyme farnesyltransferase, cleavage of the terminal 3 amino acids (SIM) by Zmpste24, and carboxymethylation by the enzyme isoprenylcysteine carboxymethyltransferase (ICMT). A second and final cleavage by Zmpste24 removes the terminal 15 amino acids and the farnesyl group, allowing mature lamin A to be inserted into the lamina. In contrast, because of its 50-aa internal deletion, progerin lacks the second cleavage site and thus remains permanently farnesylated. Reproduced with permission from “Mechanisms of cardiovascular disease in accelerated aging syndromes.” by B. C. Capell, F. S. Collins and E. G. Nabel, 2007, Circulation Research, 101, p. 16. Copyright 2007 by Wolters Kluwer Health, Inc.

Patients with Progeria have some normal lamin A production. De Sandre-Giovannoli, Bernand, Cau et al (2003) showed 25% normal lamin A in HGPS lymphocytes. However, research by Reddel & Weiss (2004) showed that that 60% of the lamin A is normal and 40% is progerin, this was attributed to the fact that HGPS mutation in one allele contributes 40%
of the progerin found and 7% of the total normal lamin A protein transcript, while the wild-
type allele contributes approximately 53% of normal lamin A protein (Figure 2).  

![Diagram of DNA-LMNA gene showing wild-type and mutant alleles with transcription and splicing events](image)

**Figure 2. Quantitative schematic showing new hypothesised model of allelic expression and abnormal splicing event in HGPS cells.**


Thus, in HPGS there is normal lamin A production, but at a decreased level.

However, it is the presence of progerin that results in the Progeria phenotype and not the decreased level of lamin A. Research by Fong et. al. (2006) using a knockout mouse model showed that at least in mice prelamin A and lamin A are dispensable, and lack of lamin A did not result in disease.  

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Cellular Changes in Progeria

Nuclear blebbing is the characteristic change noted at the cellular level in HGPS (Figure 3). This seems to be the result of incorporation of progerin to the nuclear lamina resulting in increased thickness and alteration of the nuclear structural properties. HGPS cells subsequently become stiffer, it is thought that this might result in altered cellular response when exposed to mechanical stress (Figure 4).

Figure 3. High magnification examples of the extracted boundary curvature of a blebed, HGPS nucleus, and a more oval, normal nucleus (scale bar: 10 μm). Adapted from "Automated image analysis of nuclear shape: what can we learn from a prematurely aged cell?" by M. Driscoll, J. Albanese, X. Xiong, et al, 2012, Aging (Albany NY), 4, p. 121. Copyright 2012 by M. Driscoll et al.

Figure 4. Lamin distribution and DNA in fibroblasts from HGPS patients. Control primary fibroblasts, when fixed and labeled with an antibody for lamin A/C, show homogeneous distribution of lamins at the nuclear envelope with some lamins at the nuclear interior. The DNA, labeled with DAPI, is relatively evenly dispersed throughout the nucleus except for exclusion from the nucleoli. Cells from patients with HGPS (from the Progeria Research Foundation) at passage 12 begin to show redistribution of lamins to the nuclear membrane as well as an altered nuclear morphology. DNA is also redistributed heterogeneously throughout the nucleus. The scale bar is 20 μm. Reproduced with permission from "Mechanobiology and the microcirculation: cellular nuclear and fluid mechanics" by K. N. Dahl, A. Kalinowski and K. Pekkan, 2010, Microcirculation, 17, p. 185. Copyright 2010 by John Wiley and Sons.
Lamins normally participate in chromatin organization and function, additional changes seen at the cellular level in HGPS relate to chromatin structure and epigenetic markers. In HGPS there are also defects in DNA repair as a result of reduced DNA damage response (DDR) factors and slowed repair kinetics.

Research utilizing a mouse model showed that Zmpste24-deficient mice exhibit profound nuclear architecture anomalies and an accelerated aging phenotype similar to what is seen in Lmna-deficient mice. Using the same animal model there is upregulation of p53 and of a stress signal pathway. Zmpste24-deficient mice also have dysregulation of the somatotrophic axis via transcriptional alteration in genes, as well as high levels of circulating growth hormone (GH) and decreased levels of plasma insulin-like growth factor 1 (IGF-1). Also there is upregulation of the microRNA 29 family. These Zmpste24-deficient mice also have alterations of lipid and glucose metabolism, resulting in an alternated metabolic response that includes activation of intracellular autophagy.

Zmpste24-deficient mice and Lmna<sup>G609G</sup>/G609G mice, which is knock-in mouse strain that carries the most frequent HGPS mutation, have NF-κB activation and secretion of pro-inflammatory cytokines via ATM- and NEMO-dependent signaling pathways. Moreover, NF-κB inhibition prevents the age-associated features of those two animal models. In addition, research using HGPS fibroblasts has demonstrated p53 over activation, as well as persistent DNA damage checkpoint activation. Telomere function is also affected in HGPS, in HGPS fibroblasts proliferative defects were suppressed with expression of the catalytic subunit of telomerase (hTERT). In fact, research by Kudlow, Stanfel, Burtner, Johnston, & Kennedy (2008) demonstrated that in HGPS fibroblasts p53 inhibition or hTERT expression resulted in suppression of early proliferative defects associated with progerin. Research by Benson, Lee & Aaronson (2010) has shown that telomerase extends HGPS lifespan via p53 and Rb
pathway activation. In HGPS attrition of adult stem cells has been observed, as well as alteration in the number and proliferative capacity of epidermal stem cells, and alteration of signaling pathways. RanGTPase regulates nucleocytoplasmic transport by controlling assembly and disassembly of nuclear transport complexes. HGPS fibroblasts have defects in importing large protein complexes due to disruption in the Ran nuclear/cytoplasmic distribution.

**Clinical Characteristics of Disease**

Children with Progeria can appear normal at birth, but by the first year of life they start displaying features of the disease. Clinical features include short stature, delayed growth, micrognathia, craniofacial disproportion, alopecia, prominent eyes and scalp veins, and lack of subcutaneous fat, giving the skin an aged appearance (Figure 5). Patients with Progeria have normal intelligence. However, patients with Progeria develop progressive atherosclerosis, which is the main cause of mortality. Merideth et al., in their 2008 paper reviewing the phenotype and course of HGPS, noted that many children are hyperopic and that some experience dry eye and keratopathy.
Figure 5. Physical Findings in Children with Hutchinson–Gilford Progeria Syndrome.

Growth and Development

Delayed growth is one of the characteristic features of progeria manifested by lipoatrophy and wasting of limbs. The average weight gain after the 2\textsuperscript{nd} year of life is 0.44 Kg/year and remains fairly constant throughout life, which is significantly less than age-matched normal children. Birth length tends to be normal, but within the first year of life length falls below the 3\textsuperscript{rd} percentile for thereafter. Moreover, children with Progeria
develop knee flexion contractures resulting in height underestimation. As a result, children with Progeria reach a final weight of approximately 14 Kg and a height of 1 meter. \(^\text{11,45}\)

**Cardiovascular & Cerebrovascular Disease**

Cardiovascular disease is a major source of mortality in patients with HGPS in the form of myocardial infarction (90%) and cerebrovascular accidents (10%). \(^\text{46}\) Children with Progeria have significant cardiovascular disease starting as early as 3 years of age. \(^\text{44}\) Patients with Progeria have both small and large vessel disease including plaque formation and adventitial fibrosis (Figures 6, 7), \(^\text{47}\) as well as atherosclerosis, vascular occlusive disease leading to hypertension, cardiac valve insufficiency, cardiomegaly and congestive heart failure (Figure 8). \(^\text{11,48}\)

![Figure 6. Fibrosis of the adventitia in HGPS.](image)

H&E staining of selected tissues from patient HG001 (A) and HG120 (B-C). A, Aorta with thickened adventitia (arrow). B, Mid-right coronary characterized by an enlarged and highly fibrotic adventitia (arrow). The media is markedly thinned in the area with adventitial fibrosis. C, High-power image of the adventitia (arrow) in B. D, 16-year-old non-HGPS aorta with non-diseased adventitia (arrow). E, 16-year-old non-HGPS LAD, F, 93-year-old LAD with advanced atherosclerosis. The arrow head points to the adventitia. Adventitia: ad, media: m. (Scale bars: A,C-D: 50 μm; B,E-F 500 μm). Reproduced with permission from "Cardiovascular Pathology in Hutchinson-Gilford Progeria: Correlation With the Vascular Pathology of Aging" by M. Olive, I. Harten, R. Mitchell, et al., 2010, *Arteriosclerosis, Thrombosis, and Vascular Biology*, 30, p. 2303. Copyright by Wolters Kluwer Health, Inc.
Figure 7. ECM deposition in HGPS lesions is similar to that seen in adult CAD. Coronary artery sections were stained for collagen with Picrosirius Red (A, F, K, P), decorin with LF122 (B, G, I, Q), versican with 2B1 (C, H, M, R), hyaluronan (D, I, N, S) and macrophages with CD68 (E, J, O, T). Collagen was imaged using a polarizing filter to distinguish between Type I (orange/red staining) and Type III (green/yellow staining). Black arrow heads refer to patterns of decorin, versican and hyaluronan staining indicative of healed plaque rupture. Vessel lumen: lu, adventitia: ad, media: m, intima: i, calcium deposition: ca, necrotic core: nc. (Scale bars: 100 μm). Reproduced with permission from “Cardiovascular Pathology in Hutchinson-Gilford Progeria: Correlation With the Vascular Pathology of Aging” by M. Olive, I. Harten, R. Mitchell, et al., 2010, Arteriosclerosis, Thrombosis, and Vascular Biology, 30, p. 2304. Copyright by Wolters Kluwer Health, Inc.

Figure 8. Vascular, Bone, Dental, and Auditory Findings in Children with Hutchinson–Gilford Progeria Syndrome.

In Panel A, the markers show the borders of plaque in the common carotid artery in Patient 15. Panel B shows the vascular lesion (arrow) in the carotid artery in Patient 15. Panel C shows acro-osteolysis in Patient 14 at 12 years of age. Distal phalanges show resorption to tufts. Panel D shows clavicular resorption and the conical chest in Patient 13 at 10 years of age. Panel E shows the coxa valga in Patient 13. The angle of the acetabulum with respect to the femur is reduced. The left hip joint is characterized by destruction and displacement. Panel F shows high-grade stenosis (arrows) at the level of the carotid siphons bilaterally in Patient 14. Panel G shows the ogival palate in Patient 9. Panel H shows the composite audiogram of the right ear, indicating low-frequency hearing loss in 11 patients with Hutchinson–Gilford progeria syndrome. The black line indicates the mean air-conduction threshold for the right ear, and the orange line indicates the bone-conduction threshold for the right ear. Reproduced with permission from “Phenotype and course of Hutchinson-Gilford Progeria Syndrome” by M. A. Merideth, L. B. Gordon, S. Clauss, et al, 2008, New England Journal of Medicine, 358, p. 595. Copyright Massachusetts Medical Society.
Patients can experience dyspnea on exertion and angina. 60% of patients with HGPS by the age 14 have features of cerebrovascular infarcts on neuroimaging. In the same study, Silvera et al. (2003) noted precavernous and supraclinoid internal carotid artery stenosis and less frequently of the anterior and middle carotids. In addition, vertebral artery stenosis of the distant V2/proximal V3 segment was noted, there was also significant collateral vessel formation in a distinctly different fashion from what is observed in normal aging. Patients with Progeria had significantly more intracranial than neck arterial disease. Vascular anomalies that have not been observed include aneurysmal formation, arterial dissection, arteriovenous malformations, arteriovenous fistulas, sinus thrombosis and subarachnoid hemorrhages. Of note patients with progeria are of normal intelligence and there have been no reported cases of Alzheimer disease or dementia.

Dermatologic Features

Patients with HGPS have similar sclerodermatous skin features that appear before the first year of life, especially involving the abdomen and lower extremities. These include loss of subcutaneous fat, stippled skin pigmentation, circumoral cyanosis, areas of skin tightening, dystrophic nails, gradual scalp and brow alopecia, and madarosis. Children with Progeria have characteristic prominence of scalp and body superficial veins (Figures 5, 9). Alopecia is another universal finding in Progeria, children are born with normal hair texture but there is progressive alopecia starting at a mean age of 10 months. Initially it involves the temporal occipital areas, while the midscalp and vertex areas do not get
involved until a lot later in the disease, until total alopecia (Figure 9). In additional to alopecia patients with HGPS will have progressive madarosis and loss of brow hair (Figure 10). \(^{1,7,45,50}\)

**Figure 9. Progression of scalp alopecia in HGPS.**

(A) Normal hair texture and distribution at 1 week. At 7 weeks (B) and 8 weeks (C), development of hair thinning, especially in the temporal area. At 8 months (D), hair loss continues to progress, involving the occipital area. By 2 years (E and F), the patient has nearly complete scalp alopecia with the exception of the midscale and vertex areas. Superficial scalp and forehead veins are prominent. Complete scalp alopecia with thinning of the eyebrows has developed by age 3 years (G and H). Reproduced with permission from “Initial Cutaneous Manifestations of Hutchinson-Gilford Progeria Syndrome.” by J. F. Rork, J. T. Huang, L. B. Gordon, M. Kleinman, M. W. Kieran and M. G. Liang, 2014, *Pediatric Dermatology*, 31, p. 200. Copyright 2014 by John Wiley and Sons.

**Figure 10. Progression of eyebrow and eyelash loss in HGPS. Photographs are from a single patient.**

At 2 years (A) eyebrows and eyelashes are present. By 3 years (B), the eyebrows have markedly thinned with loss of the upper eyelashes. Reproduced with permission from “Initial Cutaneous Manifestations of Hutchinson-Gilford Progeria Syndrome.” by J. F. Rork, J. T. Huang, L. B. Gordon, M. Kleinman, M. W. Kieran and M. G. Liang, 2014, *Pediatric Dermatology*, 31, p. 201. Copyright 2014 by John Wiley and Sons.
Musculoskeletal Features

Children with HGPS have significant musculoskeletal morbidity as a result of a unique pattern of skeletal dysplasia (Figures 8, 11).

Figure 11. Differences in bone structure and geometry in patients with Hutchinson-Gilford progeria syndrome (HGPS) versus healthy controls.
This figure outlines some of the unusual cross-sectional geometries observed in the HGPS patients. The left panel highlights a star-shaped cross section for the radius and ulna at 20% distance from the distal growth plate in comparison with the more elliptical cross sections of the bones from a control subject. The panel on the right denotes a tailed ulnar cross section at a distance of 66% from the distal growth plate, where the medullary cavity is filled with bone. This is in sharp contrast to the site-matched cross-section from a control subject. Reproduced with permission from "Hutchinson–Gilford progeria is a skeletal dysplasia" by C. M. Gordon, L. B. Gordon, B. D. Snyder, et al, 2011, Journal of Bone and Mineral Research, 26, p. 1674. Copyright 2011 by John Wiley and Sons.

Children with Progeria have multiple characteristic skeletal changes including progressive, bilateral coxa valga, as well as clavicular resorption, distal phalangeal resorption, a receding mandible and short stature. In addition, middle ear bony anomalies, as well as a stiffer tympanic membrane can lead to low tone conductive hearing loss in patients with Progeria. The combination of skin and ligamentous changes in Progeria leads to joint contractures. The skeletal dysplasia observed in Progeria is the result of abnormal development of bone in the setting of adequate dietary intake.

HGPS Diagnosis

Previously the diagnosis of HGPS was a clinical one, however since the identification of LMNA gene responsible for HGPS in 2003 genetic testing has become available including targeted mutation analysis and sequence analysis. Moreover, the Progeria Research Foundation (http://www.progeriaresearch.org/diagnostic_testing.html) can arrange for genetic testing at a CLIA*-approved laboratory for children who are suspected to have
Progeria. Even though HGPS is an autosomal dominant disease with complete penetrance, somatic and gonadal mosaicism has been observed, the recurrence risk for a future sibling to a child with Progeria is estimated to be one in 500. 

*Clinical Laboratory Improvement Amendments (CLIA) is a set of standards passed by the United States Congress in 1988 to improve the quality of clinical laboratory testing.

**Progeria Management**

**Current General Management**

Because of the increased morbidity and mortality patients with Progeria require comprehensive disease management. Current guidelines recommend multi-system evaluations. In general medication dosing should be based on weight and body surface area, and not age.

Children with Progeria should have their first dental evaluation by year one of life with return visits every 6 months for prophylaxis and fluoride treatments as cavities are frequent. Moreover, children with Progeria can have crowding and eruption disturbances requiring orthodontic treatment and extractions.

Children with Progeria tend to have mild low-to-mid frequency conductive hearing loss without a significant impact in hearing and language development. Patients should have yearly audiological evaluation to detect hearing loss into the speech frequencies. Preferential seating in the classroom might be required or the use of hearing aid.

**General growth and musculoskeletal evaluations**

Patients should have regular weight and height monitoring, yearly bone mineral density evaluations using dual energy X-ray densitometry with size adjusted Z-scores, bone structure can also be evaluated using peripheral quantitative computed tomography. Skeletal X-rays for evaluation of acro-osteolysis, clavicular resorption, avascular necrosis and
coxa valga should also be performed. Children with Progeria should maintain a healthy, regular diet that ensures adequate calcium and vitamin D intake. Oral supplementation with 400 IU of Vitamin D is recommended. Lack of adequate soft tissue support and padding of the feet is a cause of significant foot and gait problems for children with Progeria, because of this the use of custom shoe inserts is recommend, as well as the use of moisturizing lotions for calluses. Children with Progeria should have a yearly evaluation by a podiatrist. Moreover, routine physical and occupational therapy evaluations should be conducted. Children with Progeria should remain physically active with appropriate modifications of their exercise routine with avoidance of passive exercises due to increased risk of joint dislocation.

**Cardiovascular Care**

Cardiovascular disease is a frequent cause of morbidity and mortality in children with Progeria, therefore at a minimum a yearly cardiac evaluation should be conducted. In addition to heart rate and blood pressure monitoring of arms and legs, children should have fasting glucose and lipid laboratory evaluations, as well as an electrocardiogram and echocardiogram. Where available baseline carotid artery duplex ultrasounds and pulse wave velocity measurements should be obtained. Because of increased cardiovascular mortality associated with general anesthesia the recommendation is to be used only if absolutely necessary. Patients undergoing anesthesia should have careful fluid and blood pressure management, moreover intubation can be difficult due to a narrow airway and retrognathia.

**Neurologic Care**

Cerebrovascular disease and strokes are also one of the most frequent causes of morbidity and mortality in children with Progeria, strokes can occur as early as 4 years of
age. In addition, transient ischemic attacks (TIA) can also occur. As mentioned earlier 50% of patients will have silent strokes. Because of this magnetic resonance imaging (MRI) and magnetic resonance angiography of the head and neck (MRA) at baseline and at regular intervals is recommend to monitor for infraction and to better evaluate the vascular structures. If seizures were to occur, then an electroencephalogram (EEG) is recommend. Children with Progeria complain of frequent headaches, this is thought to be secondary to vascular disease. Also, headaches can be triggered by certain foods, as well as lack of sleep.

Neurologic symptoms can be triggered as a result of dehydration; thus, children should be kept well hydrated. Aspirin can be used at baseline to decrease the risk of stroke. In case of acute stroke or TIA patients should be admitted, possibly in an intensive care unit to maintain cerebral perfusion and adequate blood pressure. Antiplatelet agents can be used; aspirin can be dosed at 3-5 mg/Kg per day.

Headaches can be managed symptomatically by staying in a quiet, darkly lit room, hydration and with the use of nonsteroidal anti-inflammatory medications or paracetamol. Common headache triggers should be avoided, these include chocolate, cheese, nuts, shellfish, sugar, caffeine, alcohol, and foods containing monosodium glutamate (MSG) commonly found in Chinese food.

**Developing Therapies & Clinical Trials**

Understanding of the post-translational modifications lamin A and progerin undergo has resulted in multiple possible therapeutic interventions for progeria (Figures 1 & 12).
Figure 12. Progerin post-translational processing pathway and potential target points for treatment. Enzymes shown in green; enzyme inhibitors shown in red; solid arrow, single step; dashed arrow, multiple steps; FT, farnesyltransferase; ICMT, S-isoprenylcysteineO-methyltransferase. Reproduced with permission from “Hutchinson–Gilford progeria syndrome” by N. J. Ullrich, & L. B. Gordon, 2015, Handbook of Clinical Neurology, 132, p. 257. Copyright 2015 by Elsevier.

**Farnesyltransferase Inhibitors**

The discovery of *LMNA* gene mutation that is responsible for Progeria in 2003\footnote{4}\footnote{5} provided a target for possible treatments and in just 5 years since that discovery the first human clinical trial for Progeria was launched (ClinicalTrials.gov identifier, NCT00425607).\footnote{56}

The mutant prelamin A remains farnesylated and accumulates in the nuclear membrane resulting in “blebbing” (Figures 3, 13).\footnote{4}\footnote{26} In addition, inhibition of farnesylation was independently evaluated in the field of cancer research in an effort to alter ras regulation.\footnote{58}

Farnesyltransferase inhibitors (FTIs) bind the CaaX domain of proteins and prevent farnesylation (Figure 12). It has been found that when progerin farnesylation is inhibited by
FTIs progerin does not get incorporated to the nuclear membrane. In vitro studies of FTIs have shown resolution of the typical nuclear changes seen in Progeria within 36 hours (Figure 13).

**Figure 13. Cultured human fibroblast nuclei demonstrating nuclear morphology.**

In vivo studies using HGPS mouse models have shown significant benefits from the use of FTIs, this includes reduction of bone fractures, improvement in weight gain and life span, as well as vascular pathology which is the biggest cause of mortality in HGPS.

Since 2007, 3 on-going clinical drug trials are being conducted at Boston Children’s Hospital (ClinicalTrials.gov identifiers, NCT00425607, NCT00879034, and NCT00916747). The initial clinical trial evaluated prospectively 25 children with HGPS that were treated with the oral FTI lonafarnib for a minimum of 2 years. Patients had improvements in weight gain, vascular stiffness, radial bone structural rigidity and sensorineural hearing, moreover there was decrease in stroke and headache frequency, and the estimated lifespan also increased by 1.6 years. However, there were no changes in bone mineral density, insulin resistance, dermatologic and dental symptomatology.
**Statins and aminobisphosphonates**

Zmpste24-deficient mice exhibit a similar phenotype to Lmna-deficient mice, as well as nuclear architecture. Even though FTIs improve progeroid phenotypes they do not completely eliminate them. Prelamin A and progerin have been shown to undergo alternative prenylation by geranylgeranyltransferase in the setting of farnesyltransferase inhibition, which could explain the low efficiency of FTIs. The combination of statins and aminobisphosphonates inhibits farnesylation via the farnesyl pyrophosphate pathway (Figure 12), as well as geranylgeranylation. In vivo studies using a mouse model deficient in the metalloproteinase Zmpste24 have shown that combined treatment with the statin pravastatin and the aminobisphosphonate zoledronic acid results in significant improvements of progeroid phenotypes and lifespan. More specifically there was improvement in growth retardation, weight loss, lipodystrophy, hair loss and bone defects. These findings have led to the incorporation of pravastatin and zoledronic acid in clinical trials for the treatment of Progeria (ClinicalTrials.gov identifier, NCT00879034).

**Methylation Inhibitors**

A possible therapeutic pathway for treating progeria targets the carboxymethylation part of the posttranslational modification of lamin A. Part of the normal posttranslational modification of both prelamin A and progerin involves the enzyme isoprenylcysteine carboxymethyltransferase (ICMT), which is responsible for methylation of farnesylcysteine following the cleavage of the terminal three amino acids by Zmpste24 (Figures 1, 12). In a progeroid Zmpste24-deficient mouse with a hypomorphic ICMT allele that results in 70-90% decreased ICMT activity, there was significant improvements in disease phenotypes including increased body weight, normal grip strength, prevention of bone fractures and
death. Moreover, ICMT knockdown in human HGPS fibroblasts prevented premature senescence.\textsuperscript{70}

**Rapamycin**

Rapamycin is a macrolide antibiotic that has been shown to expand lifespan and improve cardiovascular parameters during in vivo studies utilizing aging mice models. More specifically Rapamycin in Progeria acts after progerin has been formed by accelerating progerin clearance via autophagy and leads to delay of senescence. Moreover, there is reduction of nuclear blebbing and reduction of progerin moieties in the cellular nucleus.\textsuperscript{71,72,73}

**Resveratrol**

The NAD\textsuperscript{+}-dependent protein deacetylase SIRT1 regulates multiple cellular metabolic pathways.\textsuperscript{74} In the presence of progerin there is reduced SIRT1 interaction with the nuclear matrix and decreased deacetylase activity causing rapid depletion of adult stem cells in Zmpste24-deficient mice. Resveratrol, which is a natural compound derived from red grapes acts as a deacetylase SIRT1 activator and enhances its binding with lamin A and progerin, resulting in rescue of adult stem cell decline. In vivo studies using resveratrol in the Zmpste24-deficient mouse model has led to improvements in cellular phenotypes (decrease in weight loss, improved bone structure and mineral density) and lifespan.\textsuperscript{75}

**Gene Therapy**

Given that Progeria is almost exclusively caused by a single de novo nucleotide substitution at position 1824 (C $\rightarrow$ T) of the LMNA gene in the long arm of chromosome 1\textsuperscript{4,5} causing the activation of an alternative pre-mRNA splice site, it becomes an ideal candidate for gene therapy via different pathways.
One option would be deletion or inhibition of this alternative splice site. This has been achieved both in vitro and in vivo with a knockin HGPS mouse model via a morpholino oligonucleotide (exo11) that is complementary to the region containing the HGPS mutation in exon 11 blocking activation of the activated cryptic splice site, leading to phenotypic rescue. The in vivo approach actually resulted in improved weight gain, lifespan and improvements in phenotypes.

Another option would be to prevent progerin synthesis via gene silencing using RNA interference (RNAi). This could potentially be performed by short interfering RNA (siRNA), which are 21-22 nucleotide long double-stranded RNA fragments that interact with a multi-protein RNA-Induced Silencing Complex (RISC), that contains the AGO2 endonuclease. The RISC eventually bind to target mRNA and AGO2 causes RNA degradation.

Recently targeted gene therapy using an adeno-associated virus in HGPS patient-derived induced pluripotent stem cells (HGPS-iPSCs) has been achieved. The targeted gene therapy approach with adenoassociated virus has been successfully used in ophthalmology in human clinic trials for the treatment of Leber congenital amaurosis secondary to RPE65 mutations, this was achieved via subretinal injection of an adeno-associated virus carrying the RPE65 gene (ClinicalTrials.gov identifiers, NCT00999609 and NCT01496040). Additional gene therapy trials are being conducted for the treatment of Stargardt disease using a lentivirus vector carrying the ABCA4 gene (ClinicalTrials.gov identifier, NCT01367444), choroideremia using an adeno-associated virus as a vector for the REPI gene (ClinicalTrials.gov identifier, NCT 01461213), X-linked retinoschisis (ClinicalTrials.gov identifiers, NCT02416622 and NCT02416622) and Leber hereditary optic neuropathy (ClinicalTrials.gov identifiers, NCT...
01267422, NCT02161380, and NCT02064569) both using adeno-associated virus vectors.  

It is well established that HGPS patients do not show central nervous system deterioration, including dementia.  In addition, microRNA miR-9 has been shown to downregulate lamin A and progerin synthesis in the brain.  A targeted approach harnessing this protective function of mRNA could potentially be used in the future.  

Recent developments utilizing the genome editing technology clustered regularly interspaced short palindromic repeat (CRISPR)/Cas9 are promising as a possible way for LMNA gene repair. In fact, this technique has been used in one-cell human embryos to correct point mutations in the HBB and G6PD genes.  

*Stem Cell Treatments*

Stem cell deficiency is well documented to occur in HGPS, as well as in the Zmpste24-null progeroid mouse model. Stem cell therapy is already being used to manage various types of leukemia and lymphomas, blood dyscrasias, and severe combined immunodeficiency among other conditions. Overall it is viewed as a promising way of managing disease and certainly Progeria is not an exception.  

*Ophthalmic Changes Attributed to Aging*

Aging is strongly associated with eye disease and ocular tissue dysfunction, and advanced age is a significant risk factor for multiple eye diseases. Presbyopia, dry eye, cataracts, glaucoma, and age-related macular degeneration (AMD) have significantly higher incidence and prevalence with advanced age. There are numerous cellular, inflammatory, structural and physiologic changes that occur with aging that contribute to age-related ophthalmic pathology.
**Presbyopia**

Loss of accommodation and development of presbyopia is a hallmark of aging. During accommodation, the refractive power of the lens changes and allows the eye to focus on objects at a range of distances. The near point is defined as the point at which accommodation is maximally exerted. Presbyopia occurs when the near point recedes beyond a comfortable reading distance, most people become symptomatic around the 4th decade of life.\(^9^7\) It is thought to be the result of progressive increase in the lens stiffness as a result of decline in lenticular protein crystalline, as well as possible alternation of ciliary muscle contraction and zonular attachments.\(^9^8\)\(^9^9\) Presbyopia has been managed with various ways including reading glasses, monovision, multifocal lenses, corneal inlays, scleral implants, refractive laser surgery, and more recently with the use of accommodating intraocular lenses (IOL).\(^1^0^0\)\(^1^0^1\)\(^1^0^2\)\(^1^0^3\)\(^1^0^4\)\(^1^0^5\)\(^1^0^6\)

**Ocular Surface Disease**

Aging causes changes to the ocular surface, by affecting both the cornea and ocular adnexa.\(^9^3\)

Pterygia become more common with aging.\(^1^0^7\) Ultraviolet radiation and oxidative stress appear to be key factors in the pathogenesis of both pterygia and conjunctivochalasis.\(^1^0^8\)\(^1^0^9\)\(^1^1^0\)\(^1^1^1\) Moreover, aberrant DNA methylation has been demonstrated in pterygia,\(^1^1^2\) as well as induction of inflammation and abnormal cell cycle regulation leading to defective apoptosis.\(^1^1^3\)\(^1^1^4\)\(^1^1^5\)\(^1^1^6\)\(^1^1^7\)\(^1^1^8\)\(^1^1^9\)\(^1^2^0\)

Dry eye prevalence increases with age.\(^1^2^1\) Oxidative stress appears to also be important in meibomian gland dysfunction and dry eye seen with aging.\(^1^2^2\)\(^1^2^3\) Meibomian gland dysfunction causes tear film instability and increased evaporative tear loss, leading to
Dry eye symptoms are further compounded by senile associated decrease in tear production by the lacrimal glands. Advanced age is associated with increased corneal epithelial permeability, which can increase the risk of infection as the corneal barrier function is compromised. In addition, with aging there is a gradual decline in the number of corneal endothelial cells, which increases the risk of pseudophakic bullous keratopathy following cataract surgery and also increases the risk of damage during hypoxic injury. Corneal endothelial cell death with aging seems to be related to reduced ability to handle oxidative stress.

**Cataract**

Cataract remains the most common cause of blindness in the world with regional differences in incidence. Even though cataract formation is multifactorial, age remains a significant risk factor, other etiologies of cataracts include genetic causes, medications, diabetes, radiation, and trauma. Denaturation of lens proteins from oxidative stress is a major cause of age related lenticular changes.

Lens fibers are unique because they undergo extreme differentiation, including removal of nuclei and cessation of protein synthesis. Crystallins are the main lens proteins and are responsible for the refractive properties of the lens. The human lens is one of the few body sites where these “long-lived” proteins can be found. Other locations where “long-lived” proteins can be found include the lungs and brain. Cataract formation occurs as a result of progressive denaturation of crystallins from aging that causes decrease in lens clarity, “yellowing,” hardening and opacification of the lens.

Crystallins are subdivided in α-, β- and γ-crystallins. α-crystallins have 2 subunits: αA-αB- and exist in the lens in a 3:1 ratio. They act as heat shock proteins that are important
during cellular exposure to elevated temperature, inflammation, ischemia and hypoxia. The αA-crystallin subunit is found in human lenses, while αB- is also found in heart, lungs, central nervous system, skin and skeletal muscle.\textsuperscript{137} Crystallins inhibit apoptosis in lens epithelium cells and cells that overexpress α-crystallins are more resistant to a variety of external stressors including thermal, osmotic and oxidative; crystallin absence is associated with aging phenotypes,\textsuperscript{138 137 139} while mutations in the Cryab gene that encodes αB-crystallin is associated with neurologic, cardiac and muscular disease.\textsuperscript{137} More importantly, the appearance of αB-crystallin in cerebral cortex neurons appears to be associated with Alzheimer’s disease, a disease strongly associated with aging.\textsuperscript{140} Moreover, αB-crystallin seems to be also be associated with skeletal muscle aging, as it has been found that animal models of sarcopenia have elevated αB-crystallin and other heat shock proteins.\textsuperscript{141} Thus, it is possible that lenticular changes could be used at some point as bio-indicators for other aging phenotypes.\textsuperscript{142}

Senile cataracts can be subdivided in three types: nuclear, cortical and posterior subcapsular (PSC). Nuclear cataracts occur centrally and are the result of progressive changes in the lens fiber proteins especially from oxidation, this results in increased light scattering and lens pigmentation.\textsuperscript{143 144 145 146 147 148} Cortical cataracts on the other hand occur in the lens periphery and can appear as spoke-like and vacuolated. Cortical cataracts are thought to be the result of osmotic changes from ionic imbalances resulting in water accumulation within the lens cells. Damage to the cellular membrane ion pumps that maintain the physiologic ionic gradient results in influx of water in lens cells. The water vacuoles have a different refractive index than the rest of the lens fiber cytoplasm resulting in light scattering. Finally, posterior subcapsular cataracts occur under the posterior lens capsule. They can form as a result of abnormal lens fiber differentiation and migration of
lens cells to the posterior pole. Chronic steroid use and radiation therapy are common causes of PSC cataracts.\textsuperscript{134}

Oxidation of the sulfur containing amino acids cysteine and methionine in human lens cells is a feature of cataractogenesis.\textsuperscript{149,150} Oxidative stress in human lens epithelial cells results in accelerated DNA damage, telomere shortening and finally senescence of lens cells.\textsuperscript{151,152} Glutathione is important in protecting the lens from oxidative damage and its concentration is noted to be reduced in cataracts.\textsuperscript{153,154} In addition, exposure to high oxygen levels appears to be a factor in cataract formation from oxidative stress.\textsuperscript{148} For example, hyperbaric oxygen treatment and vitrectomy surgery (during which there is increased oxygen exposure to the lens) are both associated with nuclear cataract formation.\textsuperscript{155,156,157,158,159}

Oxidative stress also leads to mitochondrial dysfunction which also has been implicated in cataract formation,\textsuperscript{160} while increased antioxidant intake seems to be protective for the formation of age-related cataracts.\textsuperscript{161,162}

Finally, the role of micro RNA (miRNA) in cataract formation has also been explored, it seems that there is differential miRNA expression in lens epithelium cells in transparent and cataractous human lenses.\textsuperscript{163} Let-7b miRNA appears to be a risk factor in the formation of senile cataracts,\textsuperscript{164} while the MIR204 miRNA appears to have a significant role in the anterior segment of the eye by regulating apoptosis, endoplasmic reticulum stress response and inflammation.\textsuperscript{165}

Retinal Changes with Aging & Age-Related Macular Degeneration

There are well demonstrated structural and functional age-related changes to the retina stemming from chronic light-induced damage to retinal cells. Aging is accompanied
by loss of rods, ganglion cells, bipolar cells, as well as retinal pigment epithelium cells. Other structural retinal changes that are seen with aging include intracellular accumulation of lipofuscin in the retinal pigment epithelium (RPE), which acts as a free radical generator with formation of reactive oxygen species when exposed to light and oxygen. There is also progressive accumulation of deposits, including esterified and unesterified cholesterol in Bruch’s membrane, which is related to the accumulation of drusen between the RPE and Bruch’s membrane which in turn is key feature of nonexudative Age-Related Macular Degeneration. Electrophysiologic studies have demonstrated reduced dark adaptation thresholds, as well as a linear decline in retinal scotopic and photopic responses with aging. In addition, there seems to be decreased efficiency of photopigment restoration with advanced age as demonstrated by electroretinography (ERG) photostress testing.

As the name implies Age-Related Macular Degeneration (AMD) is seen in elderly patients and it is the leading cause of blindness in patients over 65 years of age, especially of European descent. It is estimated that the prevalence of AMD will reach 2.95 million in the United States by the year 2020. AMD has a genetic basis, but it is influenced by multiple factors including age, race, sex, family history. Smoking, hypertension, obesity and dietary fat intake have also been associated with AMD, this is most the result of epigenetic modulation leading to altered gene expression and phenotypic expression.

Macular degeneration is characterized by the presence of drusen, which are lipid-rich deposits, in the subretinal space between the RPE and Bruch’s membrane. Drusen can be further classified according to their size as small, medium and large, as well as by their margins either as soft or hard. AMD manifests in two forms, nonexudative (also known as
dry AMD) and neovascular (also known as wet AMD). Nonexudative AMD is characterized by RPE degeneration, photoreceptor loss and geographic atrophy (GA); dry AMD is responsible for 90% of cases. Vision loss in dry AMD is usually slow that can progress over years. Nonexudative AMD can progress to the neovascular form, which is characterized by breaks in Bruch’s membrane, choroidal neovascular membrane (CNVM) formation and hemorrhage with exudation of subretinal fluid eventually leading to photoreceptor loss and scar formation. Patients with wet AMD can have rapid vision loss, even though the wet type of AMD accounts for a smaller portion of the total cases of AMD, it is responsible for up to 80% of severe vision loss associated with AMD.

Numerous cellular pathways that are influenced by aging have been implicated in the pathophysiology of AMD with mitochondrial dysfunction, oxidative damage, immune dysregulation and inflammation having key roles. RPE dysfunction is central to AMD pathogenesis, with RPE atrophy preceding geography atrophy in dry AMD and choroidal neovascularization in wet AMD.

Oxidative injury and oxidative protein modifications appear to be important in drusen formation and in the pathogenesis of AMD. Mitochondrial dysfunction and formation of reactive oxygen species (ROS) has been implicated in AMD. Mitochondria are highly concentrated in photoreceptors given the high oxygen demands of the retina, in AMD there is greater loss of RPE mitochondria with aging, and there is also an association between certain mitochondria DNA haplotypes and AMD. ROS form during endogenous mitochondrial metabolism, while exogenous ROS are formed as a result of exposure to light and toxins. A vicious cycle between ROS and mitochondrial dysregulation exists with aging as ROS can lead to mitochondrial DNA mutations, which in-turn lead to
mitochondrial dysfunction and increased ROS production. The relationship between oxidative stress and mitochondrial dysfunction has also been implicated in cataract formation (see section for Ophthalmic Changes with Aging/Cataract). Lipofuscin accumulation in RPE has been well demonstrated in AMD, when exposed to light it leads to ROS formation. Drusen have been found to have increased concentration of oxidation products, including carboxyethylpyrrole protein adducts and carboxymethyl lysine. Carboxyethyl pyrrole adducts are uniquely generated from the oxidation of docosahexaenoate-containing lipids, which are found in photoreceptor outer segments, while carboxymethyl lysine is generated by carbohydrate oxidation and is an advanced glycation end product (AGE). The same carboxyethylpyrrole modified proteins have been shown to lead to drusen accumulation below the RPE and production of lesions that mimic geographic atrophy in a mouse model, via an immune mediated pathway that includes complement component-3 localization in Bruch’s membrane and lytic changes in RPE cells.

Advanced glycation end products (AGEs) are a heterogenous group of macromolecules formed by the non-enzymatic glycation of proteins, lipids and nucleic acids. Endogenous AGEs are formed as part of aging; this process is accelerated in diabetes. AGEs can lead to an increased inflammatory response and oxidative stress by activation of the receptor for advanced glycation end products (RAGE). AGEs have been found in drusen, they accumulate on Bruch’s membrane, as well as in RPE and photoreceptors of patients with AMD. Glycoxidation products and RAGE have been found in subretinal membranes in patients with AMD, while the RAGE-mediated pro-inflammatory response is important in retinal para-inflammation.

Para-inflammation is a tissue adaptive response to noxious stress or malfunction and has characteristics that are intermediate between basal and inflammatory states.
inflammation and is an important process in retinal aging and in the pathophysiology of retinal degeneration, it is associated with complement activation in Bruch’s membrane and RPE, inflammatory cytokine/chemokine production, microglial activation with subretinal migration, as well as blood-retinal barrier breakdown that can lead to retinal injury. 207 Para-inflammatory responses may be triggered by oxidative stress and AGEs. Complement dysregulation has been implicated in AMD, 208 while a complement factor H variant is associated with increased risk for developing AMD. 209 210 211

Recently the ribonuclease enzyme DICER1 has been found to be important in maintaining appropriate RPE function, by modulating inflammation and RNA expression. Patients with advanced dry AMD with geographic atrophy were found to have reduced DICER1 levels, while conditional ablation of DICER1 induces RPE degeneration in mice. 212

Alu elements are the most common small interspersed repetitive elements in the human genome, compromising 11% of the human genome, and can alter gene expression and cause insertional mutagenesis. 213 214 It seems that DICER1 deficiency leads to overabundance of Alu transcripts, as normally DICER1 silences Alu transcripts. 215 Alu elements can also increase as a result of stress, including heat shock. 216 A strong relationship between DICER 1, Alu elements and immunomodulation seems to exist, as it has been shown that in experiments using donated eyes from patients with geographic atrophy from AMD, DICER1 deficit or Alu RNA exposure causes NLRP3 inflammasome activation, which results in RPE IL-18 secretion and induction of MyD88-dependent RPE cell death; 215 while NLRP3 inflammasome can also occur by complement C1q, which is present in drusen. 217
The role of vascular endothelial growth factor-A (VEGF-A) in the pathophysiology of wet AMD was realized in the past 20 years\textsuperscript{218,219} and resulted in the development of new treatment modalities for wet AMD.\textsuperscript{220,221,222,223} As in dry AMD inflammation and oxidative stress are also important in the development of wet AMD by modulation of choroidal neovascularization. RPE produces and secretes VEGF-A in response to complement\textsuperscript{224,225} and oxidative stress.\textsuperscript{226} In addition, oxidative stress can also trigger an immune response by causing complement activation and deposition in the retina.\textsuperscript{199,227} Just as important appears to the role of macrophages in choroidal neovascularization, as choroidal neovascularization is associated with increase in retinal macrophages\textsuperscript{228,229,230} and abnormal macrophage activation might occur as the result of lipid found in drusen.\textsuperscript{231} Aging macrophages tend to be of the M2-like phenotype with an altered cytokine profile that seems to contribute to aberrant inflammation and inability to inhibit abnormal angiogenesis.\textsuperscript{232}

**Glaucoma**

Glaucoma is a group of optic neuropathies characterized by progressive degeneration of retinal ganglion cells and is associated with elevated intraocular pressure.\textsuperscript{233} Clinically it manifests by “cupping” of the optic nerve and leads to vision loss, first peripherally and then centrally. Glaucoma is the leading cause of irreversible blindness in the world and the second cause of blindness in the United States.\textsuperscript{234} Open angle glaucoma represents 80\% of glaucoma cases in the United States.\textsuperscript{235} In addition to family history and black race, advanced age is a significant risk factor for the development of primary open angle glaucoma (POAG).
The pathophysiology of open angle glaucoma is not entirely understood, but the end result is retinal ganglion cell (RGC) loss.\textsuperscript{236} Elevated intraocular pressure is a major risk factor for the progression of POAG,\textsuperscript{237} which can lead to mechanical stress at the level of the lamina cribrosa\textsuperscript{238,239} where the RGC axons exit the eye.\textsuperscript{240} This can cause mechanical damage to the RGC axons, as well as disruption of axonal transport and disruption of retrograde axoplasmic flow of neurotrophic factors which can trigger RGC apoptosis.\textsuperscript{241,242}

Increased resistance at the level of the trabecular meshwork is a major cause for elevated intraocular pressure.\textsuperscript{233} There are well documented structural changes that occur at the trabecular meshwork (TM) in patients with glaucoma, these changes include foamy degeneration with basement membrane thickening of the TM endothelial cells,\textsuperscript{246} increase in glycosaminoglycans,\textsuperscript{247} accumulation of nonfibrillar material in the juxtacanalicular part of the TM and changes in extracellular lysosomes.\textsuperscript{248,249} It is thought that some of the ultrastructural changes seen in glaucoma could represent accelerated aging changes.\textsuperscript{250}

RGC death associated with multiple cellular mechanisms that are linked to aging, including oxidative stress,\textsuperscript{251,252} mitochondrial dysfunction,\textsuperscript{253} and glutamate-mediated excitotoxicity.\textsuperscript{254} The interplay between mitochondrial dysfunction, oxidative stress and aging is well demonstrated in ophthalmic disease, including cataract formation and macular degeneration (see sections for Ophthalmic Changes with Aging/Cataract and for Ophthalmic Changes with Aging/Retinal Changes with Aging & Age-Related Macular Degeneration). Similar processes seem to also occur in glaucoma, including mitochondrial DNA mutations and mitochondrial dysfunction.\textsuperscript{253} In addition to having a role in macular degeneration (see section for Ophthalmic Changes with Aging/Retinal Changes with Aging & Age-Related...
Macular Degeneration) AGES are also associated to glaucoma. Aging is also linked to AGES accumulation in the lamina cribosa, which might be related to glaucomatous optic neuropathy and RGC degeneration. Moreover, AGES have been shows to have an effect on senescence, oxidative stress and induction of apoptosis of trabecular meshwork cells. Finally, vascular mechanisms that are related to aging have been invoked in the pathophysiology of glaucoma, these are reduced ocular perfusion and vascular endothelial dysfunction.

**Part Two**

**Rationale and Hypothesis**

There have been case reports describing the ophthalmic manifestations of children with Progeria and other premature aging syndromes; in their seminal paper describing the HGPS phenotype Merideth et al (2008) noted that patients with Progeria tended to be hyperopic and that some experienced dry eye and keratopathy. Patients with other premature aging syndromes, including Cockayne and Werner's syndrome, have been noted to have early onset cataracts and even retinal vasculitis, while patients with xeroderma pigmentosum have been noted to have squamous and basal cell carcinoma of the lids, as well as significant ocular surface disease including pterygia, pinguecula, dry eye and keratopathy with conjunctivalization of the cornea. In contrary, there have been no reports of cataracts, macular degeneration and glaucoma in patients with Progeria. Based on this, it was felt that patients with Progeria will have ophthalmic disease affecting at least the ocular surface, and it would be important to evaluate if they exhibit early presbyopia, cataracts, glaucoma and macular degeneration. However, given
the rarity of Progeria there has been no systemic reporting of the ophthalmic features of Progeria. Thus, the main goal of the study was to establish the ophthalmic natural history for this ultra-rare genetic disease.

Methodology

A natural history, retrospective case series of patients with Progeria who were seen at Boston Children’s Hospital between 2007 and 2016 was conducted. This study was approved by the Institutional Review Board of Boston Children’s Hospital and conformed to the requirements of the United States Health Insurance Portability and Accountability Act. Some clinical information was obtained from The Progeria Research Foundation’s Medical and Research Database, which is approved by the Institutional Review Boards of Rhode Island Hospital and Brown University. Since 2007, three ongoing clinical drug trials are being conducted at Boston Children’s Hospital (ClinicalTrials.gov identifiers, NCT00425607, NCT00879034, and NCT00916747).57 68 Children from around the world have been referred by The Progeria Research Foundation to participate in those clinical trials. Children participating in those research trials with eye complaints have been evaluated by myself at the Department of Ophthalmology (Table 1). In addition, clinical treatment trial patients who were not seen at the Department of Ophthalmology at Boston Children’s Hospital, but for whom detailed clinical ophthalmologic records were available, were also included for analysis. In total 14 patients from 10 countries with complete ophthalmic examinations were identified for this study. One clinical trial patient was excluded due to a paucity of ophthalmic history in his clinical record. The patient’s age, sex, and clinical findings were abstracted from the medical record. Thirteen of the 14 patients had the classic form of Progeria, caused by a single de novo nucleotide substitution in exon 11 of the LMNA gene,
c.1824C>T/p.G608G, while one patient had a non-classic progerin-producing mutation in intron 11 of LMNA, c.1968+1 G>A consistent with atypical HGPS.1 269

Table 1. Components of the Ophthalmologic Exam

| Age-appropriate Visual Acuity (Snellen, LEA, HOTV, grading acuity) |
| Dynamic retinoscopy |
| Cycloplegic refraction |
| Sensorimotor evaluation (Extraocular motility, alignment, stereopsis) |
| Pupillary responses |
| Visual fields |
| Intraocular pressure measurement |
| Corneal sensation |
| External and slit-lamp exam |
| Indirect dilated fundus exam |
| Retinal optical coherence tomography (OCT) |

Results

A total of 14 patients (28 eyes) were included for statistical analysis from a total of 84 patients who have been enrolled in clinical trials for Progeria at Boston Children’s Hospital; this essentially represents an estimated 20% of the world’s known patients with Progeria. Seven of 14 (50%) of the patients were male. Mean age of presentation was 7.4 years. Length of follow-up ranged from a single visit to 5 years (Table 2).

Table 2. Patient Demographics (N=14)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 14 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>7/14 male (50%)</td>
</tr>
<tr>
<td>Age at Initial Ophthalmic Exam</td>
<td>7.4 years (range 2.5-16.4 years; SD: 4.27)</td>
</tr>
<tr>
<td>Length of Follow-up</td>
<td>0.94 years (range: single visit-5 years; SD: 1.57)</td>
</tr>
</tbody>
</table>

SD: Standard deviation
Most patients complained of ocular surface disease. Specifically, the majority of patients (12/14 patients, 93%) reported nocturnal lagophthalmos, followed by ocular irritation (12/14 patients, 86%), photophobia (11/14 patients, 79%), tearing (9/14 patients, 64%), redness of the eyes (6/14 patients, 43%), history of eye infections (6/14 patients, 43%), and blurry vision (5/14 patients, 36%). Twenty-nine percent reported spectacle use (Table 3).

### Table 3. Ophthalmic Symptomatology

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Incidence, N (%) (N= 14 Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal Lagophthalmos</td>
<td>13/14 (93%)</td>
</tr>
<tr>
<td>Ocular Irritation</td>
<td>12/14 (86%)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>11/14 (79%)</td>
</tr>
<tr>
<td>Tearing</td>
<td>9/14 (64%)</td>
</tr>
<tr>
<td>Red Eyes</td>
<td>6/14 (43%)</td>
</tr>
<tr>
<td>Previous Eye Infection</td>
<td>6/14 (43%)</td>
</tr>
<tr>
<td>Blurry Vision</td>
<td>5/14 (36%)</td>
</tr>
<tr>
<td>Spectacle Use</td>
<td>4/14 (29%)</td>
</tr>
</tbody>
</table>

On clinical examination, most patients had good visual acuity, with best-corrected visual acuity (BCVA) better than 20/40 using the Snellen chart (Table 4). Counting eyes, 17 of 28 (61%) had BCVA greater than 20/40, 8 of 28 eyes (29%) had BCVA between 20/40 and 20/80, while 1 of 28 eyes (4%) had BCVA less than 20/80. Visual acuity could not be recorded in one patient (two eyes) due to noncooperation. Twenty-two of 28 eyes (79%) were hyperopic, with a mean spherical equivalent of +1.90 diopters (range -0.75 to +4.75 diopters). Sixteen of 28 eyes (57%) were noted to have astigmatism, with a mean value of 0.95 diopters (range 0.25 to 2.00 diopters). Of the eyes with astigmatism, all were noted to have with-the-rule astigmatism (defined as plus cylinder within 20 degrees of the 90-degree axis). Of interest, 5 of 10 patients (50%) who had their accommodation evaluated via
dynamic retinoscopy had delay. Twelve of 14 patients (86%) had their stereoacuity evaluated which was noted to have a mean value of 90 seconds of arc (range 30-300 seconds of arc).

**Table 4. Refractive Characteristics**

<table>
<thead>
<tr>
<th>Best-Corrected Visual Acuity</th>
<th>Data for N=14 Patients/28 eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/20 to 20/30</td>
<td>17/28 eyes (61%)</td>
</tr>
<tr>
<td>20/40 to 20/70</td>
<td>8/28 eyes (29%)</td>
</tr>
<tr>
<td>≤ 20/80</td>
<td>1/28 eyes (4%)</td>
</tr>
</tbody>
</table>

| Mean Spherical Equivalent (range) | +1.90 D (-0.75 to +4.75) |
| Mean Astigmatism (range)         | 0.95 D (0.25-2.00)        |
| Mean Stereoacuity (range)        | 90 seconds of arc (30-300) |

Most patients had clinically significant findings on external examination; these included shallow orbits in 26 of 28 (93%) eyes, 1-2 mm lagophthalmos with exposure keratopathy in 22 of 28 (79%) eyes (Figure 14), sparse (2/28; 7% eyes) and absent (20/28; 71% eyes) brow hair, and madarosis in 14 of 28 (50%) eyes (Figure 15).

![Figure 14. Trace lagophthalmos of the right eye and 0.5 mm lagophthalmos of the left eye in a 6-year-old.](image-url)
Figure 15. Absent brow hair, madarosis and inferior corneal scar secondary to exposure keratopathy in an 8-year-old.

Slit lamp examination revealed significant pathology as well. Eleven of 28 (61%) eyes had corneal scarring (Figures 15, 16); in 3 patients the corneal scarring was bilateral. More impressively, in 4 eyes (3 patients) there was associated corneal thinning, ranging from 10% to 50% (Figure 16). Fortunately, none of the patients had experienced corneal rupture. Of the 2 patients who had their corneal sensation evaluated, one patient’s was intact while the other patient had reduced corneal sensation bilaterally. The patient with the reduced corneal sensation also exhibited exposure keratopathy with lagophthalmos and had sustained corneal ulceration with secondary corneal scarring. Additionally, aggressive pterygia were noted in 3 eyes (2 patients, ages 7 and 10 years old). Both patients were from geographic areas associated with significant sun exposure. The pterygia were observed and managed non-operatively; however, overall the aggressiveness of the pterygia was out of proportion to what is typically seen in the pediatric age group (Figure 17). Essentially...
all patients who exhibited corneal pathology had bilateral signs and symptoms. This was true for ocular irritation, exposure keratopathy, and punctate corneal epithelial erosions.

Figure 16. Madarosis, 10% inferior corneal thinning and scarring secondary to corneal ulcer in a 5-year-old patient.

Figure 17. Extensive pterygium involving the visual axis of the left eye of a 12-year-old.
A 12-year-old patient with Progeria developed an acute unilateral orbital hematoma following a cold with associated coughing (Figure 18) that was managed non-operatively and resolved without complications.

Figure 18. 7-year-old with acute left orbital hemorrhage.
A. Mild left eye proptosis and ecchymosis of the upper and lower eyelids.

B. High-resolution coronal T1-weighted magnetic resonance image (MRI) of the orbits reveals extraconal superior orbital hemorrhage (black arrow) with surrounding inflammatory changes.
C.
None of the patients were noted to have manifest strabismus, cataracts, glaucoma, or retinal pigmentary changes suggestive of a retinal degeneration. OCT and fundus photos of patients with Progeria show normal foveal contour, retinal vessels of normal caliber and course, as well as absence of drusen and retinal pigmentary changes (Figures 19, 20).

Clinical findings of the patients are summarized in Table 5, while Figure 21 presents the age for which there was the first report for the following symptoms and signs of ophthalmic disease: Prominent eyes, lagophthalmos, tearing, eye redness, photophobia, absent brow hair, corneal infection, corneal scarring, corneal ulceration, subjective ocular irritation, madarosis, and pterygium.

**Table 5. Clinical Findings**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N (%) Eyes (N=28 Eyes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prominent Eyes</td>
<td>26 (93%)</td>
</tr>
<tr>
<td>Lagophthalmos with Exposure</td>
<td>22 (79%)</td>
</tr>
<tr>
<td>Madarosis</td>
<td>14 (50%)</td>
</tr>
<tr>
<td>Corneal Scarring</td>
<td>11 (39%)</td>
</tr>
<tr>
<td>Corneal Thinning</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Pterygia</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Orbital Hematoma</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>
Figure 19. Fundus photos of the right and left eye of a 5-year-old patient with HGPS showing normal optic nerve, retinal vascular and macular anatomy.

Figure 20. OCT of the retina of a 14-year-old HGPS patient showing normal foveal contour (Top: Right eye. Bottom: Left eye).
Figure 21. Age at which HGPS patients first presented with ophthalmic symptomatology and signs of eye disease.

**Discussion**

Hutchinson-Gilford Progeria syndrome is a genetic condition that results in premature aging; it is associated with significant systemic morbidity, and patients die at a mean age of 14.6 owing to associated complications. Progeria is ultra-rare with an incidence of 1 in 4 million; it has an estimated worldwide prevalence of 1 in 20 million living individuals with approximately 350–400 living children with Progeria worldwide, 30% of whom are currently identified through The Progeria Research Foundation International Registry.

Case reports have been published regarding the ophthalmic manifestations of premature aging syndromes. In their seminal paper, Merideth and associates described the clinical characteristics of 15 children with Progeria who were enrolled in a comprehensive clinical protocol; the ophthalmic findings were briefly presented and were
notable for most children being hyperopic and 5 of 15 (33%) having corneal dryness. The research conducted as part of this thesis provides detailed findings of the ophthalmic manifestations of HGPS. In the diverse cohort that was evaluated, most patients with Progeria complained of ocular symptoms, including ocular irritation and photophobia. Often these complaints were severe enough to negatively affect quality of life, as was verified by their caregivers. A significant portion of patients complained of having previous episodes of eye infections, including sequential and frequent episodes of corneal ulcers.

Patients with Progeria are at risk for significant ocular morbidity that can lead to vision loss. In this cohort, 11 out of 28 (39%) evaluated eyes had corneal scarring, and 9 of 28 (33%) of eyes had BCVA less than 20/40. Most of the ocular pathology noted was secondary to ocular surface disease and exposure keratopathy. Corneal scarring was unilateral in 5 patients and bilateral in 3 patients. However, all patients with corneal scarring had bilateral corneal surface disease, including punctate epithelial erosions and exposure keratopathy from lagophthalmos. Most patients exhibited nocturnal lagophthalmos and on clinical examination punctate corneal epithelial erosions were present in the inferior one quarter to one third of the cornea, corresponding to the exposed cornea. The earliest report of nocturnal lagophthalmos in this cohort was at 5 months of life, whereas for corneal scarring the earliest report was at 5 years of age. One of the two patients who had their corneal sensation evaluated (which was noted to be reduced), also had a history of corneal exposure keratopathy, history of corneal ulceration and secondary corneal scarring. This raises the possibility that the corneal ulceration exhibited was multifactorial, mostly owing to exposure keratopathy but also perhaps due to decreased corneal sensation. It is also possible that a component of the ocular surface disease
exhibited in patients with Progeria is a result of corneal stem cell deficiency. The corneal limbal stem cells are responsible for maintaining and renewing the corneal epithelium.\textsuperscript{273, 274} Patients with corneal limbal stem cell deficiency can have significant ocular surface disease, manifested by recurrent and persistent corneal epithelial defects leading to corneal scarring and neovascularization. These patients are at risk for corneal ulceration and perforation. Symptomatically, patients exhibit decreased vision, photophobia, tearing, and redness.\textsuperscript{275} Corneal epithelial limbal stem cells are derived from embryonic ectoderm.\textsuperscript{276} In an HGPS-related animal model using Zmpste24-null progeroid mice, stem cell dysfunction has been demonstrated.\textsuperscript{40} In these mice there is alteration in the number and proliferative capacity of epidermal stem cells, as well alteration of signaling pathways that regulate stem cell behavior. In addition, using an inducible HGPS mouse model, Rosengardten and associates demonstrated depletion of epidermal adult stem cells and impaired wound healing.\textsuperscript{41} In addition, Wenzel and associates were able to isolate naïve multipotent skin-derived precursor (SKP) cells from pre-existing dermal fibroblast cultures that had been obtained from children with HGPS and were able to detect progerin in HGPS-SKP cells.\textsuperscript{89} Moreover, SKP cells can self-renew and also differentiate into fibroblasts and smooth muscle cells (SMCs). The number of progerin-positive SMCs derived from these HGPS-SKP cells increased dramatically with each passage, consistent with accumulation of progerin with increased cellular age. All findings support the idea that progerin may have a significant role in adult stem cell dysfunction.\textsuperscript{89} Epidermal stem cells are also derived from ectoderm,\textsuperscript{277} so it is possible the stem cell abnormalities that have been described in epidermal stem cells in Progeria are also present in corneal epithelial limbal stem cells.

In this study, 4 eyes with corneal scarring also had associated corneal thinning. This
can be an independent risk factor for corneal rupture following mild blunt trauma. Even though this has not been reported in HGPS, it has been reported in a patient with Wiedemann-Rautenstrauch syndrome, a neonatal progeroid syndrome, following an innocuous, low-impact fall. 

It is interesting that 2 patients developed very aggressive pterygia (Figure 16). Pterygia form as a result of ultraviolet-B exposure, and multiple pathways have been implicated in their formation, including oxidative stress and DNA damage, defective regulation of apoptosis, induction of inflammatory and angiogenic mediators, growth factor stimulation, and altered immunologic responses. Histologic characteristics of pterygia include squamous metaplasia and decreased apoptotic markers. In Progeria several defects of DNA repair, cell-cycle deregulation, and changes in inflammatory pathways have been noted; these could explain why aggressive pterygia were formed in our patients. More specifically, in pterygia markers of oxidative DNA damage are elevated, including 8-hydroxydeoxyguanosine, while in Progeria defects in DNA repair have been observed as a result of reduced DNA damage response factors and slowed repair kinetics. The tumor suppressor p53, as a checkpoint of proliferation and apoptosis induction, has been found to be elevated in pterygia, and research using the progeroid animal model of Zmpste24-deficient mice has shown upregulation of p53 and of a stress signaling pathway. Finally, inflammatory mediators are induced in pterygia, including interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor-α, cyclooxygenase-2, and phospholipase D. In Progeria there may be a component of increased inflammation; NF-κB activation and secretion of proinflammatory cytokines via ATM- and NEMO-dependent signaling pathways has been observed using 2 different Progeria mouse models.
Even though most patients had what was thought to be age-appropriate hyperopia, a significant portion (4/14 patients, 29%) were in spectacle correction to improve visual acuity. More significantly, 5 of the 10 patients who were evaluated with dynamic retinoscopy exhibited accommodation delay. In addition, the stereoacuity of patients with Progeria was less than what is expected for children of that age without Progeria. Decreased accommodation could be the result of decreased zonular laxity and might indicate premature presbyopia.

Progeria patients in our cohort did not develop the typical ophthalmic changes seen with aging, including cataracts, glaucoma and macular degeneration. Patients with Cockayne and Werner syndrome are known to develop cataracts, but this was not the case for HGPS patients in this study. This may be the result of the tissue and cell specificity of lamin A, an inner nuclear membrane protein expressed primarily in differentiated cells such as fibroblasts, vascular smooth muscle cells, and vascular endothelial cells. Considering that the typical intracellular changes in Progeria involve the nucleus, and most lens fibers are devoid of a nucleus, one would not expect to see lenticular changes in Progeria. In one study, senile cataracts were not associated with LMNA mutations, nor was the normal lamin A protein truncated. Moreover, keeping in mind the common embryologic origin of the retina, optic nerve, and brain, and the fact that patients with Progeria do not show central nervous system deterioration such as dementia, it is reasonable to consider that there could be a common pathway protecting against macular degeneration and glaucomatous optic neuropathy. One possible regulatory pathway involves the microRNA miR-9, which downregulates lamin A and progerin synthesis in the brain and is a key regulator of developmental timing in the vertebrate retina. MiR-9
is expressed in retinal pigment epithelial cells in humans, and in mice it is preferentially expressed in retina and brain, but not in other tissues.

By studying the ophthalmic manifestations of patients with Progeria, it could potentially allow us to gain insight into ophthalmic changes that occur with normal aging.

Not all the typical ages seen with aging can be found in Progeria. As mentioned earlier patients with HGPS do not have dementia, and there is lack of cataracts, glaucoma and macular degeneration. In addition to lack of dementia in patients with Progeria, there is lack of tumors. This is especially impressive given the increased incidence of tumors with aging, as well as by the fact that most of the cellular damage that occurs in Progeria happens at the nuclear level. It seems there is a protective mechanism in HGPS against cancers, using a ZMPSTE24 mosaic mouse model it has been showing that prelamin A accumulation prevents oral carcinoma infiltration. This is possibly the result of activation of tumor suppressors including p53 in HGPS.

As an accelerated aging model HGPS is already being used to better understand how aging affects different body systems and processes at the cellular level, and to help develop newer treatments for aging. This is possible because of similarities between Progeria and normal aging, both at the molecular level, as well as in presentation and symptomatology. Even normal individuals can have progerin present in their tissues, albeit at a significantly lower percentage. In fact, progerin has been found to accumulate in dermal fibroblasts and terminally differentiated keratinocytes with normal aging. There are significant similarities in cardiovascular pathology and of the atherosclerotic plaques in patients with HGPS and in the elderly, in addition progerin can be found in coronary arteries of non-HGPS individuals. Moreover, the peripheral vascular occlusive disease and the
vascular stiffening seen in HGPS is similar to that seen in the general aging population.\textsuperscript{44} Also, prelamin A seems to have a role in promoting vascular smooth muscle cell calcification by disrupting mitosis and inducing DNA damage.\textsuperscript{296,297} Finally, as mentioned earlier (see sections for Molecular Pathogenesis/Cellular Changes in Progeria & Progeria Management/Developing Therapies & Clinical Trials/Stem Cell Treatments), HGPS is associated with stem cell dysfunction which is similar to what is seen with normal aging as well.\textsuperscript{40,41,298}

The possibility of using eye exam findings as a marker of aging or for systemic diseases associated with aging is not a foreign concept in ophthalmology. Retinal changes have been noted in neurodegenerative disease, specifically decrease in retinal nerve fiber layer thickness (RNFL) has been linked to Alzheimer’s disease and spinocerebellar ataxia,\textsuperscript{299} while in Parkinson’s disease there is inner retinal layer thinning and decrease in accommodation.\textsuperscript{301,302} Even more impressive has been the work of Dr. Lee E. Goldstein who discovered a specific type of cataract rich with amyloid beta deposits in the cytoplasm of equatorial supranuclear cortical lens fiber cells in the far periphery of patients with Alzheimer’s disease,\textsuperscript{303} in fact a similar link has been found in Down syndrome. Because patients with Down syndrome have triplication of the APP gene on chromosome 21 that encodes the Alzheimer’s disease amyloid precursor protein,\textsuperscript{304} there is APP overexpression resulting in excess deposition of amyloid beta in the brain and the lenses of patients with Down syndrome.\textsuperscript{305} Dr. Goldstein’s group has now created a quasi-elastic light scattering scanning laser ophthalmoscope that can noninvasively detect Alzheimer disease-linked protein differences in the lenses of patients with Down syndrome.\textsuperscript{306}
ophthalmologic clinical features of patients with Progeria, it is also important to share my clinical approach to the management of ocular surface disease. In this cohort, the youngest patient to have ophthalmic symptoms was 5 months old. In addition, corneal scarring was noted to be present as early as 5 years of life. As a result, an annual eye examination is recommended starting at the time of diagnosis. Because most of the pathology seems to be secondary to exposure keratopathy, aggressive lubrication with artificial tears and gel at night is advised. In addition, tape tarsorrhaphy at bedtime for patients with significant nocturnal lagophthalmos is recommended. The use of punctal plugs can be considered in older patients who are more cooperative. I have been hesitant to pursue surgical management of pterygia and lagophthalmos unless the eye disease is vision threatening, mainly owing to the increased risk of cardiovascular complications from general anesthesia in patients with Progeria. For patients who have corneal thinning, the use of protective polycarbonate glasses to minimize the risk of blunt ocular trauma that could lead to globe rupture is recommended.

The main limitations of this study are obviously its retrospective nature and the rarity of the disease. The patients who were included in this study were already enrolled in a clinical trial of lonafarnib, a farnesyltransferase inhibitor. However, I do not believe that this treatment would have a clinical impact on ocular surface disease. There is a selection bias regarding which patients were included in the study, as not all the patients who are part of the Progeria research trials were included. The patients who were referred for an eye exam were patients that were already experiencing ocular pathology when they came for their study visit. Patients who are part of the clinical research trial for Progeria come to Boston Children’s Hospital for 5 days and have multiple evaluations; it was felt that
it would be an undue burden to subject all study participants to an eye exam if they did not have any pathology. Another limitation of our study is that 3 of the patients who were included were not seen by myself, but I was able reviewed the records from their primary ophthalmologist. Given the ultra-rare nature of the disease, including these patients in this study of ophthalmic manifestations of Progeria was deemed appropriate as it would add invaluable information. The clinical records from their ophthalmologist were detailed and in many cases I communicated directly with the patient’s primary ophthalmologist. Finally, the ocular pathology noted was easily detected on slit-lamp examination, a skill that all ophthalmologists are comfortable with.

Future directions could include a prospective study of ophthalmic manifestations of patients with Progeria and to access a possible link between the ophthalmic changes seen in Progeria and aging. In addition to what is typically evaluated as part of the ophthalmic exam, patients could also undergo corneal impression cytology,\textsuperscript{307} this would allow detection of possible corneal limbal stem cell deficiency and to evaluate if the stem cell dysfunction that is seen patients with Progeria is also found in their corneal limbal stem cells.\textsuperscript{41 88 89} Moreover, spectral-domain OCT of the anterior segment could be used to evaluate the morphology of the palisades of Vogt,\textsuperscript{308} while corneal confocal microscopy would detect changes in keratocyte density and morphology.\textsuperscript{309} Even though there have no macroscopic observations of cataractous changes in patients with Progeria, it would be great to evaluate the lenses of HGPS patients with the quasi-elastic light scattering scanning laser ophthalmoscope to detect possible Alzheimer disease-linked protein in their lenses.\textsuperscript{306} Finally, OCT scanning of the optic nerve and retina would allow better characterization of
the retinal anatomy in HGPS patients and to measure subtle changes to RNFL thickness and macular ganglion cells. 310

In summary, patients with Progeria can experience significant ocular morbidity and vision loss owing to ocular surface disease. Exposure keratopathy and nocturnal lagophthalmos are significant contributing factors to the ocular surface disease, with corneal limbal stem cell deficiency and induction of inflammatory mediators possibly contributing factors. Children with Progeria should have an ophthalmic evaluation at the time of diagnosis and at least yearly after that. Aggressive ocular surface lubrication is recommended, including the use of tape tarsorrhaphy at night.
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Περίληψη

Σκοπός: Ο προσδιορισμός της οφθαλμολογικής εξέλιξης των ασθενών με προγηρία, ο καθορισμός του εύρους των οφθαλμολογικών χαρακτηριστικών τους και η ανάπτυξη περισσότερο αποτελεσματικών μεθόδων θεραπείας.

Μεθοδολογία: Ανάλυση των οφθαλμολογικών χαρακτηριστικών ασθενών με προγηρία, οι οποίοι εξετάστηκαν μεταξύ 2007 και 2016 στο Νοσοκομείο Παιδιών την Βοστώνης (Boston Children’s Hospital). 14 ασθενείς (28 οφθαλμοί) περιλήφθηκαν για στατιστική ανάλυση, από ένα σύνολο 84 ασθενών που συμμετέχουν σε κλινικές μελέτες για την προγηρία στο Νοσοκομείο Παιδιών της Βοστώνης. Ασθενείς οι οποίοι δεν εξετάστηκαν στο Οφθαλμολογικό Τμήμα του νοσοκομείου μας, αλλά για τους οποίους υπήρχαν λεπτομερείς καταγραφές των οφθαλμολογικών ευρημάτων επίσης συμπεριλήφθησαν σε αυτή τη μελέτη. Η έρευνα αυτή περιέλαβε περίπου το 20% των παγκόσμιων γνωστών ασθενών με προγηρία.

Αποτελέσματα: Τα οφθαλμολογικά ευρήματα που εντοπίστηκαν ήταν υπερμετρωπία, καθώς και σημεία νόσου της οφθαλμικής επιφάνειας οφειλόμενη σε νυκτερινό λαγόφθαλμο και έκθεση του κερατοειδούς. Επιπρόσθετα οφθαλμολογικά ευρήματα ήταν ελαττωμένη τρίχωση στα φρύδια, μαδάρωση και ελαττωμένη προσαρμοστικότητα. Οι περισσότεροι ασθενείς είχαν σχετικά καλή οπτική οξύτητα, παρόλα αυτά προχωρημένη οφθαλμική νόσος συνοδεύονταν με μειωμένη οπτική οξύτητα.

Συμπεράσματα: Παιδιά με προγηρία έχουν κίνδυνο σοβαρών οφθαλμολογικών επιπλοκών λόγω νόσου της οφθαλμικής επιφάνειας. Παιδία με προγηρία πρέπει να υποβληθούν σε οφθαλμολογική εξέταση τη στιγμή της διάγνωσης και να έχουν ετήσια επανεξέταση.
Συνιστάται σχολαστική ενυδάτωση της οφθαλμικής επιφάνειας και επίδεση κατά τη διάρκεια της νύχτας.
Abstract

**Purpose:** To establish the natural history of ophthalmic characteristics in Progeria patients by identifying the range of characteristics and to develop more effective treatments.

**Methods:** Chart review of patients with Progeria who were seen between 2007 and 2016 at Boston Children’s Hospital. 14 patients (28 eyes) were included for statistical analysis from a total of 84 patients who have been enrolled in clinical trials for Progeria at Boston Children’s Hospital. Clinical treatment trial patients who were not seen at the Department of Ophthalmology at our hospital, but for whom we had detailed clinical ophthalmologic records, were also included. This essentially represents an estimated 20% of the world’s known patients with Progeria.

**Results:** Ophthalmic manifestations noted were hyperopia and signs of ocular surface disease due to nocturnal lagophthalmos and exposure keratopathy. Additional ophthalmic manifestations included reduced brow hair, madarosis, and reduced accommodation. Most patients had relatively good acuity, however advanced ophthalmic disease was associated with reduced acuity.

**Conclusions:** Children with Progeria are at risk for serious ophthalmic complications due to ocular surface disease. Children with Progeria should have an ophthalmic evaluation at the time of diagnosis and at least yearly after that. Aggressive ocular surface lubrication is recommended, including the use of tape tarsorrhaphy at night.
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