**Lesson 321: Preanesthetic Assessment of The Patient With a Progeroid Syndrome**

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Read this article, reflect on the information presented, then go online and complete the lesson post-test and course evaluation before the termination date below. (CME credit is not valid past this date.) You must achieve a score of 80% or better to earn CME credit.

**TIME TO COMPLETE ACTIVITY:** 2 hours  
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**Professional Gaps**

While most anesthesiologists are aware of premature aging syndromes, the anesthetic implications are not as well known. Hutchinson-Gilford progeria syndrome (HGPS) and Werner syndrome (WS) are rare genetic disorders in which aspects of aging occur early on. Challenges for anesthesiologists include the potential for a difficult airway, the presence of advanced cardiovascular diseases, and multisystem derangements more typically found in the elderly. Even though they are rare disorders, their disabling and progressive nature involves frequent surgical interventions and increased anesthetic risk.

**Learning Objectives**

At the completion of the activity, the reader will be able to:

1. Describe the basic genetic characteristics of HGPS and WS
2. List the prevalence of HGPS and WS
3. Summarize the important clinical features of these disorders
4. Assess the major differences between HGPS and WS
5. Outline the characteristics of cardiovascular diseases found in these disorders
6. Identify the common causes of death in HGPS and WS
7. Explain why the progeroid syndromes are referred to as “segmental premature disorders”
8. Discuss anesthetic implications
9. Recognize the importance of preoperative evaluation
10. Present a well-designed anesthetic plan
Case

A 37-year-old white man presented for coronary artery bypass grafting, aortic valve replacement, and aortic root reconstruction for severe coronary artery disease, aortic valve insufficiency, and calcification of the aortic root. His medical history was significant for adult progeroid syndrome, hypertension (treated with lisinopril), hyperlipidemia (treated with simvastatin), and bilateral cataract surgery 7 years previously. Physical examinations revealed a patient of short stature (152 cm), low weight (46 kg), with thin gray scalp hair, dry skin, and diminished subcutaneous fat tissue. He had the characteristic pinched nose with small nares, a depressed nasal bridge, calcification under the nasal skin, and a slightly high-pitched voice. Evaluation of his airway demonstrated Mallampati class IV, a small mouth with intact dentition, and a thyromental distance of 2 finger breadths. The resting electrocardiogram was consistent with left ventricular hypertrophy and ST depression in anterolateral leads. Cardiac catheterization showed severe 3-vessel coronary artery disease with preserved left ventricular systolic function (ejection fraction, 55%-60%). Echocardiography revealed severe aortic valve insufficiency, mild mitral regurgitation, and extensive calcification of the aortic root as well as aortic and mitral valves.

Introduction

The word progeroid originates from the Greek words “pro” and “geras,” meaning “prematurely old.” The progeroid syndromes comprise a group of rare genetic disorders characterized by the appearance of accelerated aging. More than 75 syndromes involving symptoms of premature aging are now recognized. The best-studied progeroid syndromes include Hutchinson-Gilford progeria syndrome (HGPS) and Werner syndrome (WS) (Table).

<table>
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<th>Table. Differences Between Two of the More Common Progeroid Syndromes</th>
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<td><strong>Syndrome</strong></td>
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DM, diabetes mellitus; HGPS, Hutchinson-Gilford progeria syndrome; WS, Werner syndrome
HGPS was first described by Hutchinson\textsuperscript{1} and Gilford\textsuperscript{2} in England in 1886 and 1897, respectively. It also is known as progeria of childhood because clinical manifestations are usually evident by the first or second year of life. The prevalence of HGPS is estimated to be approximately 1 in every 4 to 8 million newborns. The syndrome is seen more frequently in males and whites. Death occurs in most patients before 20 years of age with the mean survival age of 13 years, usually due to myocardial infarction or, less often, stroke.\textsuperscript{3,4}

WS was identified by Werner\textsuperscript{5} in 1904 and is the most common of the progeroid syndromes. WS is often referred to as adult progeria because unlike HGPS it manifests only after the onset of puberty. The prevalence of WS in the United States is approximately 1 in 200,000 individuals, whereas in Japan and Sardinia it affects between 1 in 20,000 and 1 in 40,000 individuals, respectively, possibly due to founder mutation. Death in WS usually occurs before 55 years of age, with the mean survival age of 46 years. The major causes of death are cardiovascular complications (eg, myocardial infarction) and malignancy.\textsuperscript{6} Interest in these rare diseases has increased as research into the aging process has gained momentum.

**Genetics and Pathogenesis**

HGPS is caused by sporadic autosomal dominant mutations in the LMNA gene located on chromosome 1.\textsuperscript{7,8} The LMNA gene encodes lamin A protein, which is a prominent structural component of the nuclear lamins. The integrity of the nuclear lamins is important in maintaining the cellular function, gene expression, chromatin organization, and DNA synthesis and repair. Enormous progress has been made over the last decade in understanding the complex biology that underlies the pathogenesis of HGPS. The LMNA gene mutations result in synthesis of an alternatively toxic lamin A isoform, known as progerin.\textsuperscript{9} The accumulation of farnesylated progerin prevents the normal assembly of lamin A into the nuclear lamins. The cell nuclei from HGPS patients exhibit abnormal nuclear blebs and aberrant nuclear shapes. In vitro observations in the cultured HGPS fibroblasts showed an improved nuclear morphology, gene expression, and cellular life span following decreased formation of progerin by inhibiting farnesylation, a process that mediates posttranslational modifications of proteins and the membrane association.\textsuperscript{10} Recent clinical studies in children with HGPS reported increased survival after administration of the protein farnesylation inhibitors.\textsuperscript{11,12} Evidence is accumulating to suggest that progerin appears to be responsible for the phenotype of HGPS. However, the exact molecular and cellular mechanisms that play a role in the pathophysiology of HGPS remain to be elucidated.

WS is inherited in an autosomal recessive and non–sex-linked manner. The specific gene—WRN—responsible for WS is located on the short arm of chromosome 8 (8p12-11.2).\textsuperscript{13,14} The precise mechanisms by which mutations of the WRN gene cause the WS phenotype are unclear. Null mutations at the WRN locus are known to affect a protein (WRN), which functions as a helicase but additionally acts as an exonuclease. The WRN protein is essential for DNA repair, recombination, and maintenance.\textsuperscript{15} The genomic stability of DNA is a prerequisite for the functioning of the organ as a whole. Failure to suppress illegitimate recombination and genome instability appears to be responsible for accelerated aging and cancer predisposition in WS.

As inferred above, HGPS and WS may be regarded as models for better understanding of the biology of aging because many features of ordinary aging are present in patients with HGPS and WS.\textsuperscript{16,17} Although these patients exhibit the clinical signs and symptoms associated with aging, such as graying of the hair, osteoporosis, and atherosclerosis, there also are differences in clinical manifestations from those observed in normal aging. For example, premature cognitive decline or Alzheimer’s disease is not
present. In addition, in contrast to an increase in cancer susceptibility in individuals as they age, no increased risk for cancer is observed in HGPS. Although a patient with WS is at an increased risk for developing cancers prematurely, the neoplasms in WS tend to derive from mesenchymal cells, whereas most cancers in the elderly affect the epithelial tissue. Therefore, HGPS and WS are considered “segmental premature disorders” because they are only partially representative of the multifactorial process of normal aging.

Clinical Manifestations

Patients with HGPS and WS appear normal at birth. In HGPS, affected children begin to experience profound growth delays between 6 and 12 months of age, resulting in short stature and low weight. In contrast, the first sign in adults affected with WS is an absence of the growth spurt that normally occurs around puberty. These individuals typically reach their final height by approximately 13 years of age and are usually shorter than the general population. Signs of aging, including wrinkles, gray hair, and/or alopecia, may appear between 1 and 2 years of age in HGPS, and between 20 and 30 years of age in WS. There is a striking difference between the patient’s appearance and his or her real age in both groups.

HGPS and WS have many clinical similarities (Table). In both groups, there are substantial losses of subcutaneous adipose tissue and muscle atrophy over areas of the face and limbs. They may have a distinctive “bird-like” facial appearance including prominent eyes, a beaked or pinched nose, sunken cheeks, and a small jaw and mouth. Most patients develop a high-pitched and squeaky or hoarse voice secondary to progressive atrophy of the vocal cords. Atrophy of the skin and loss of subcutaneous tissue around the joints are associated with scleroderma-like changes and hyperkeratosis. Soft-tissue calcification and osteoporosis are frequently present. However, there are no signs of premature brain aging, and intelligence is normal in both HPGS and WS. Additional findings in HGPS include micrognathia, prominent scalp veins, dental crowding, and clavicular hypoplasia. Premature onset of senile cataracts, type 2 diabetes mellitus, hypogonadism, and leg ulceration are frequently observed in patients with WS. Of note, there is a predisposition to certain sarcomas of mesenchymal origin in WS but not in HGPS.

A severe complication in patients with HGPS and WS is progressively premature atherosclerosis, with highly accelerated calcification in the coronary arteries, aorta, and aortic and/or mitral valves. Several clinical reports described open heart procedures in patients with WS. Atherosclerosis in HGPS is widespread, affecting the aorta as well as the coronary, cerebral, and subclavian arteries, and symptoms suggestive of myocardial and cerebral ischemia usually occur late in the course of the disease, just before death.

Diagnosis

While HGPS is usually diagnosed by the second year of life, WS often may not be recognized until the third or fourth decade. Diagnosis is based on a thorough clinical evaluation, characteristic physical findings, and patient and family history. Proposed diagnostic criteria for WS include 4 cardinal signs: short stature, premature graying and/or balding, characteristic dermatologic changes, and bilateral cataracts, as well as some additional clinical signs and symptoms (Table). Urine tests may reveal elevated levels of hyaluronic acid, a complex carbohydrate present in extracellular spaces. Because production of hyaluronic acid increases with age, it is likely that the increase is a normal finding of advanced age.
The clinical diagnosis of HGPS and WS may be confirmed through genetic testing for mutations of the LMNA and WRN genes, respectively. In addition, biochemical testing with the Western blot to quantitate the amount of the WRN protein is available on a clinical basis.

**Therapy**

There are no effective treatments for HGPS and WS. Specific therapies are symptomatic and supportive, and involve a multidisciplinary team approach. The goal is to increase life span and improve quality of life by alleviating risk factors. Prognosis depends on the age-related diseases present and their severity. A healthy lifestyle should be followed. The use of low-dose aspirin is recommended as prophylaxis against atherosclerotic disease. Genetic counseling for WS is important. Prenatal screening for the WRN gene may be available to parents who are at high risk for having affected offspring.

A recent study of clinical trials in children with HGPS demonstrated that administration of protein farnesylation inhibitors reduced the toxicity of progerin and increased survival.\(^{11,12}\) Although the extent of improvement varied among patients and many clinical manifestations of the disease remained despite treatment, the study offers a first step toward life-extending HGPS therapy.

**Anesthetic Considerations**

Patients with HGPS and WS present challenges for anesthesiologists due to likely difficulty in airway management, advanced cardiovascular diseases, and multisystem derangements normally associated with advanced age. Even though they are rare disorders, their disabling and progressive nature involves frequent surgical interventions, accompanied by an increased risk for anesthetic complications. Descriptions of anesthetic management in patients with HGPS undergoing minor surgery have been reported.\(^{27-32}\) Difficulties in direct laryngoscopy with multiple attempts were observed, likely due to a small mouth opening, decreased mobility of the temporomandibular joints, and an inability to extend the neck or anterior larynx.\(^{28-30}\) Mask ventilations were performed during 5 surgical procedures secondary to either failed direct laryngoscopy\(^{29}\) or concern over postoperative laryngeal edema from a narrow glottic opening.\(^{27}\) Fiber-optic bronchoscopy was used in one patient who had previous failed intubation, which was found to be extremely difficult.\(^{29}\) There was no report of perioperative cardiac complications except for one patient who presented intraoperatively with a persistent sinus tachycardia of unknown etiology.\(^{27}\) It was noted that accounts of cardiac surgery in patients with WS have appeared in the surgical literature\(^{22-25}\) with little information about their anesthetic management.

A thorough preoperative airway evaluation should be performed, and the review of previous anesthesia records, if available, may yield useful information about airway management. Difficulty in accessing the airway is due to the craniofacial and orofacial abnormalities, including neck stiffness, poor mouth opening, and decreased mobility of the temporomandibular joint. The lack of subcutaneous tissue hinders the ability to maintain an adequate mask fit. The unpredictable degree of narrow glottic opening due to calcification may indicate the need for a smaller endotracheal tube. Nasal intubation may be difficult because of the beaked/sculpted nose. Mandibular hypoplasia, micrognathia, and poor dentition are usually present in patients with HGPS, and may contribute to a difficult intubation. Therefore, a strategy should be established beforehand, including the presence of additional personnel and the immediate availability of a difficult airway cart.
HGPS and WS are characterized by accelerated atherosclerosis, advanced coronary artery disease, severe valvular disease, and premature onset of type 2 diabetes mellitus, all of which increase the overall risk for cardiac complications. Preoperative cardiovascular evaluation includes assessment of vital signs, auscultation of heart and lungs, obtaining a resting electrocardiogram (ECG) and blood glucose, and, possibly, a glucose tolerance test. Preoperative echocardiography should be considered for determination of left ventricular systolic function and evaluation of the type and severity of valvular disease. Exercise ECG, stress echocardiography, radionuclide myocardial perfusion imaging, or coronary angiography allow further evaluation. However, preoperative coronary angiography only to confirm the existence of disease is rarely indicated. The extent of preoperative evaluation depends on the urgency as well as the risk of surgery. Children with HGPS may present with joint disease and are unable to adequately perform exercise stress testing. Previous reports have described the preoperative assessment of coronary artery disease in children using stress echocardiography and myocardial perfusion imaging. Of note, children with HGPS have normal intelligence and emotional development for their chronological age, despite the appearance of advanced age physiologically. They should be treated psychologically as children.

The appropriate level of intraoperative monitoring (eg, of arterial pressure) depends on the presence and severity of valvular and coronary artery disease as well as the assessment of left ventricular systolic function. Careful manipulation, positioning, and the protection of pressure points are important because the paucity of subcutaneous adipose tissue and muscle atrophy predispose patients to pressure sores. In addition, loss of subcutaneous adipose tissue and alopecia increase the risk for perioperative hypothermia. There is no contraindication to the use of muscle relaxants. A previous report described propofol infusion syndrome (PRIS) in a patient with Rautenstrauch-Wiedemann progeroid syndrome during surgical correction of scoliosis, suggesting a metabolic defect of mitochondria in the progeroid syndromes. The risk factors for PRIS include high-dose, long-term use of propofol and concomitant administration of catecholamines and/or steroids. It was noted that both high-dose propofol (150 mcg/kg/minute over 6.5 hours) and norepinephrine -infusions were used intraoperatively, so the implication of the study remained unclear.

Management of the Case Presented

On the morning of surgery, the patient received 2 mg lorazepam orally 1 hour before surgery. A well-equipped intubation cart, supraglottic airway device, video laryngoscope, and fiber-optic bronchoscope were readied. -Mepilex (-Möllycke Health Care) foam paddings were applied to protect all pressure points, such as the sacrum and elbows. Standard monitors were used along with a Bispectral Index (Medtronic) monitor, cerebral oximeter, and right radial artery and femoral artery catheters. In addition, a pulmonary artery catheter was used, which is our institutional but not nationwide standard of practice, and removed on postoperative day 1 without complications. Anesthesia was induced with midazolam and fentanyl in divided doses. After easy mask ventilation was assured, succinylcholine 100 mg was administered intravenously. Direct laryngoscopy with a Macintosh 2 blade revealed a grade 3 Cormach-Lehane view, with only the tips of the arytenoids visible while cricoid pressure was applied. Passage of an Eschmann introducer into the trachea was successful. A 7.5-mm endotracheal tube was placed through the Eschmann introducer without difficulty. Tracheal intubation was verified by capnography and auscultation. Intraoperative transesophageal echocardiography confirmed the preoperative diagnosis of severe aortic valve insufficiency, mild mitral regurgitation, and extensive calcification of the aortic root as well as the aortic and mitral valves. The anesthetic was maintained with a balanced sevoflurane, fentanyl, and midazolam technique along with rocuronium for muscle relaxation. Aminocaproic acid was administered as a bolus dose of 10 g over 30
minutes, followed by a continuous infusion of 2 g per hour. Three-vessel bypass graft, aortic valve replacement, and aortic root reconstruction were performed. Total cardiopulmonary bypass (CPB) time was 6 hours and 53 minutes, including aortic cross-clamp time of 5 hours and 35 minutes. Dopamine (3 mcg/kg/minute) and norepinephrine (2.5-5 mcg/minute) infusions were required for inotropic support after weaning from CPB and subsequently discontinued. Blood glucose levels increased to 360 mg/dL during CPB, and insulin infusion (1-4 units/hour) was maintained throughout the procedure. The patient exhibited diffuse oozing of blood in the surgical field after weaning from CPB. Two units of fresh frozen plasma, 20 units of cryoprecipitates, and 4 units of platelets were transfused. After adequate homeostasis was achieved, the patient was transferred to the cardiac intensive care unit in stable condition. Propofol infusion -(15-30 -mcg/kg/minute) was started before transfer for sedation and continued for approximately 11 hours. Clinical signs of PRIS (eg, metabolic acidosis or rhabdomyolysis) were not observed. The postoperative course was uneventful. He was extubated approximately 15 hours after surgery and discharged on postoperative day 7 in stable condition.

Conclusion

HGPS is an autosomal dominant genetic disorder that has an early onset by the first or second year of life, whereas WS is inherited in an autosomal recessive manner that manifests after puberty. There is a considerable interest in researching the underlying pathophysiology of the progeroid syndromes, as they may provide insight into disease mechanisms such as atherosclerosis and aspects of the normal aging process. HGPS and WS are characterized by a potential difficult airway, advanced cardiovascular diseases, and multisystem changes. The importance of preoperative recognition and definitive airway management options for ensuring adequate ventilation needs to be emphasized. Comprehensive cardiovascular assessments and intraoperative monitoring are warranted. The risk for perioperative hypothermia and pressure sores should be minimized.

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REFERENCES


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Post-test

1. Which of the following describes the inheritance pattern for Werner syndrome (WS)?
   a. Autosomal recessive
   b. Autosomal dominant
   c. X-linked
   d. Autosomal dominant with variable penetrance

2. Which of the following is the correct statement regarding the prevalence of Hutchinson-Gilford progeria syndrome (HGPS) and WS?
   a. The prevalence of WS is similar to that of HGPS.
   b. WS is the most common form of the progeroid syndromes.
   c. The prevalence of HGPS is much higher than that of WS.
   d. There are more patients with WS in the United States due to founder mutation.

3. Approximately when do clinical symptoms become noticeable in a patient with WS?
   a. At 1 to 2 years of age
   b. At 6 to 8 years of age
   c. At puberty
   d. At birth

4. The most common cause of death in WS is:
   a. cancer of epithelial origin
   b. renal failure
   c. cardiac complications (eg, myocardial infarction)
   d. diabetic ketoacidosis

5. Which of the following is a true statement about WS?
   a. Mental retardation is observed in all patients with WS.
   b. Developmental delay occurs only in 50% of patients with WS.
   c. Patients with WS have normal intellectual development.
   d. Premature cognitive decline or Alzheimer’s disease is frequently observed in WS.
6. All of the following statements concerning HGPS are true, except:
   a. HGPS is associated with dramatically premature and accelerated atherosclerosis
   b. Orofacial anatomic abnormality is one of the characteristics of HGPS
   c. Patients with HGPS require careful positioning during surgery
   d. HGPS is associated with malignant hyperthermia

7. Which of the following is not the cause of a difficult airway in patients with WS?
   a. Short thyromental distance
   b. Small mouth and jaw
   c. Narrow glottic opening
   d. Tracheomalacia

8. The calcification in WS occurs most frequently in which heart valves?
   a. The aortic and tricuspid valves
   b. The aortic and pulmonic valves
   c. The mitral and tricuspid valves
   d. The aortic and mitral valves

9. Which of the following statements is incorrect?
   a. Premature atherosclerosis is observed only in HGPS but not in WS.
   b. WS and HGPS are regarded as “segmental premature disorders.”
   c. The common causes of death in HGPS include myocardial infarction and stroke.
   d. Both WS and HGPS are characterized by premature atherosclerosis.

10. Perioperative management of patients with WS includes all of the following, except:
    a. Protection of the pressure points
    b. Use of intraoperative warming devices
    c. Careful preoperative evaluation of the airway and cardiovascular system
    d. Intraoperative invasive arterial pressure monitoring in all patients