Case Report

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HUTCHINSON-GILFORD PROGERIA SYNDROME: A RARE CASE REPORT

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ABSTRACT:

Aim: Aim of the presenting case is the rarity of this hereditary disorder.

Background: Progeria is a rare genetic disorder in which symptoms resembling combination of dwarfism and premature aging are manifested at a very early age. Most of patients born with progeria typically do not live past the age of 13 years. It is a genetic condition that occurs as a new mutation in a LMNA gene leading to formation of abnormal protein.

Case Description: A 4 year old male child patient of Indian origin reported to the Dept. of Oral Medicine and Radiology with a chief complaint of extra tooth in the midline. Extra-oral Examination revealed triangular facies, decreased subcutaneous fat deposition over the face, proptosis with entropion, beaked nose, receded chin and microstomia. Intra-Oral Examination revealed narrow V-shaped maxilla with deep palatal vault. USG, KUB, abdomen, Cranium and ECHO study were normal. On Skeletal survey, AP Skull and Lateral Skull view reveal brachycephalic skull with flattening of the occipital bone (Figure 3). X-RAY chest reveals normal bone density. Proximal bones of femur and humerus appeared longer than tibia/fibula and radius/ ulna respectively, on the bilateral lower limb X-Ray.

Conclusion: Further research on molecular etiopathogenesis of Progeroid Syndromes (PGs) is warranted so that more appropriate targeted therapy can be developed in future.

Clinical Significance: Hutchinson-Gilford Progeria Syndrome (HGPs) is the most drastic form of premature aging diseases which is characterized by multiple related features. Most of the patients die during during early teens due to cardiovascular complications.

Key words: Dwarfism, Premature Aging, Progeroid Syndrome

INTRODUCTION:

Progeroid syndromes (PSs) are a group of fatal, severe & rare genetic disorders characterized by various clinical features & phenotypes of physiological aging prematurely (Table 1). Progeria is one of the several PSs which is an extremely rare genetic disorder where symptoms related to aging are manifested at a very early stage.[1] The classic form of progeria is Hutchinson Gilford Progeria Syndrome (HGPS). The reported prevalence is 1 in 8 million births sporadically with no gender, geographical or ethnic predisposition.[2] The typical clinical features are growth

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retardation, skin atrophy, alopecia, lipodystrophy, osteolysis and increased susceptibility for malignant tumours. The average life span for these patients is 13 years (range 7-27 years).[3] The primary cause for the death in these patients is the cardiovascular complications like myocardial infarction or congestive heart failure.[2]

CASE DETAIL:

A 4 year old male child patient of Indian origin reported to the Dept. of Oral Medicine and Radiology with a chief complaint of extra tooth in the midline. He was the second child of non-consanguineous parents. Parents were healthy and normal. Pregnancy and delivery were uneventful. The mother gave history of a natal tooth which was extracted at 6th day post birth. History of bilateral reducible inguinal hernia was also present.

Patient's elder brother was under treatment for mental retardation and rickets, with no evidence of phenotypic abnormality. However, the patient did not present with mental retardation and the documented I.Q. was around 80. No other family member on paternal or maternal side was similarly affected. Patient's weight was 10 kg and the immunization history was regular.

Extra-oral Examination revealed triangular facies, decreased subcutaneous fat deposition over the face, proptosis with entropion, beaked nose, receded chin and microstomia. Maxillary hypoplasia with low set ears with deformity of both hands at bilateral elbows and wrists were evident (Figure 1).

Intra-Oral Examination revealed narrow V-shaped maxilla with deep palatal vault. Teeth present were maxillary permanent central incisors and permanent mandibular canines (Figure 2). Primary maxillary lateral incisors were palatally placed. Primary maxillary canines, primary maxillary first and second molars along with primary mandibular first and second molars were present. Crown of primary maxillary canine in the first quadrant showed evidence of cervical caries. Grossly carious tooth was seen with respect to mandibular right primary lateral incisors. Mandibular primary central incisors were congenitally missing. Microglossia was a prominent finding.

Investigations were advised to the patient. MCU (Micturating cysto-urethrogram) revealed interrupted stream of urine. It showed normal study of urinary bladder and posterior urethra. USG, KUB, abdomen, Cranium and ECHO study were normal. On Skeletal survey, AP Skull and Lateral Skull view reveal brachycephalic skull with flattening of the occipital bone (Figure 3). X-RAY chest reveals normal bone density. Proximal bones of femur and humerus appeared longer than tibia/fibula and radius/ ulna respectively, on the bilateral lower limb X-Ray. Head of femur appeared mildly superior-laterally displaced suggestive of subluxation. There was evidence of mild lateral displacement of capitulum bilaterally, suggestive of

subluxation. There was evidence of bilateral coxavalga (Figure 4). X-Ray of bilateral hands AP view showed discrepancy in the number of carpal bones i.e. four on right and six on left side (Figure 5). Thyroid function tests were normal for the patient.

DISCUSSION:

Progeria is a rare genetic disorder which is one of the several progeroid syndromes & characterized by features of premature aging at an early age. Progeria was first described in 1886 by Jonathan Hutchinson & was also described independently by Hastings Gilford.[4,5] Although progeroid syndrome refers to all the disorders characterized by premature aging symptoms however progeria specially is used in reference to HGPS. Progeroid patients are normal at birth and they develop symptoms during their first year showing reduction in growth and weight. At 10 years of age they show the characteristics of growth of a 3years old child. The clinical manifestations are bigger head, large eyes, receded jaws, thin nose, and prominent veins over the forehead & scalp, loss of hairs including eyelashes & eyebrows, & delayed teeth eruption with abnormal dentition. There is also the sclerodermatous changes and thickening of skin. Musculoskeletal degeneration leads to stiff joints, hip dislocation, and loss of subcutaneous fat. The symptoms become more pronounces as the child ages including osteolysis, lipodystrophy, hardening of arteries, renal & cardiovascular complications. The most common cause of death in these patients is due to stroke, myocardial infarction, atherosclerosis & heartfailure.[6] Moreover these patients have normal intelligence & IQ. These patients typically live to their mid-teens to early twenties.

Pathogenesis

Classical HGPS is usually caused by sporadic autosomal dominant mutation. Non-classical HGPS cases follows autosomal recessive inheritance & are characterized by less retardation of growth, slow alopecia, delayed progression of lipodystrophy & survival is mostly till adulthood.[7] This genetic condition occurs as a de novo point mutation in position 1824 of the LMNA gene, in which cytosine is replaced with thymine & is rarely inherited.[8] In a normal cell, LMNA gene codes for a structural protein called prelamin A which undergoes a series of processing steps before attaining its final form, lamin A (Flowchart 1). Lamin A is a major component of a protein scaffold on the inner edge of the nucleus (nuclear lamina) which has role in organization of nuclear processes such as RNA & DNA synthesis. Whereas in progeria there is point mutation in LMNA gene in which cytosine is replaced with thymine leading to manifestations of premature aging (Flow Chart 2). Interestingly, brain, unlike other tissues, predominantly synthesizes lamin C & very little prelamin A & thus escapes the deleterious effects of LMNA mutation. This is the probable reason of no involvement of brain in progeria patients.[9]

Diagnosis

Clinical diagnosis is made based on sign & symptoms since they are very peculiar such as skin changes, abnormal growth & alopecia. Genetic test for LMNA mutation is commonly advised for confirming the diagnosis of HGPS. Serum chemistry shows increased low density lipoproteins, cholesterol levels, hyaluronic acid (HA) level & increased urinary excretion of HA.[10] Blood investigations shows prolonged prothrombin time and elevated platelet count.[11] Skeletal survey reveals the following radiological features.[12]

- Thin & large calvarium & diploic space is absent or very shallow with conspicuous vascular markings & wormian bones.
- Short ascending rami with infantile obtuse mandibular angle.
- Delayed closure of anterior fontanelle.
- The clavicles are small in calibre & rarefied at birth.
- Ribs are abnormally gracile & posterior segments of the upper four ribs on both sides may disappear.
- Long bones are shortened & over constricted in their central part & show flares at the end.
- Coxavalga deformity is very prominent with unusual shaped greater trochanter.
- Carpal ossification centres shows osteopenia where as some shows sclerosis.

Treatment

- No treatment has yet proven effective, bur researchers are working on finding one. Treatments usually help ease or delay some of the disease's symptoms.
- Low dose aspirin can help prevent heart attacks & strokes. Coronary artery bypass surgery or angioplasty may help to slow down progression of heart disease.
- Growth hormone has been attempted. The use of Morpholinos has been attempted in order to reduce progerin production.[13,14]
- A class of cancer drugs known as farnesyltransferase inhibitors (FTIs) has shown a promise of reversing the structural abnormalities of the nucleus associated with build-up of prelamin A by restricting the activity of farnesyltransferase required to make a liaison between farnesyl groups & progerin proteins.[1] Specifically, FTIs improve the nuclear shape in the fibroblasts from the patients of PS[15] and improve nuclear blebbing in the fibroblasts of

mouse model with the gene targeted for HGPS[16]. One study has shown the prevention of both the onset and late progression of cardiovascular disease by a FTI (Tipifarnib) in a transgenic *LMNA* G608G mouse model of HGPS.[17] supporting the use of these drugs.

Varela & co-workers.[18] have shown prelamin A and its truncated form progerin/LADelta50 to undergo alternative prenylation by geranylgeranyltranferase when the farnesyltransferase was inhibited. This study has tried to explain the low efficiency of FTIs in improving the physical composition of the progeroid mouse models. They further showed that the combination of statins and aminobisphosphonates inhibited both farnesylation and geranylgeranylation of progerin and prelamin A & has improved the symptoms.

Under the partnership of Progeria Research Foundation, National Institutes of Health, Children's Hospital Boston and Dana-Farber Cancer Institute, the progeria clinical drug trial was initiated in 2010 to test the effectiveness of **three 'drugs of hope'** – **a statin drug** called Pravastatin (normally used for lowering cholesterol and preventing cardiovascular disease), **a bisphosphonate drug** called Zoledronic acid (usually used for improving osteoporosis and to prevent skeletal fractures) and **a farnesyltransferase inhibitor** called Lonafarnib (a drug that reversed progeroid associated phenotype and abnormalities in various murine models).[19] The clinical trial conducted in 25 progeroid children over two years has reported that Lonafarnib, a FTI drug, has been successful in facilitating weight gain and improving cardiovascular and skeletal pathologies.[20]

Prognosis and Future Directions

As there is no known treatment, the average life span is 13 years of age. 90% of patients die from complications of atherosclerosis, such as heart attack or stroke. As mental development is normal so intelligence tends to be average to above average. Patients do not show increased predisposition to cancer. Reproductive development is normal in these patients.

Progeria (or HGPS) is a rare syndrome which makes it difficult to study. Due to the efforts of parents of the affected children, a few research groups and the Progeria Research Foundation (PRF), the awareness of this syndrome has increased significantly. Research has also proposed probable markers for this syndrome. For example, elevated HA levels have been suggested as specific marker for HGPS.[21,22] but other studies have nullified this by reporting that urinary and serum levels of HA in HGPS patients are comparable with controls. Gordon and co-workers.[23] did a thorough analysis of the serum and urinary hyaluronidases and contravened the use of HA as a marker for HGPS. Hence, the search for an accessible and definite kind of diagnostic marker is still on.

The role of GH/IGF-1 axis in determining longevity has long been known.[24] A study has shown that DNA damage results in suppression of the GH/IGF-1 axis which in turn leads to remarkable progeroid symptoms.[25] More research on the causes and patterns of DNA damage in HGPS and ageing may provide some useful links between ageing and PS as well as normal aging process also in individuals. There is also a tremendous achievement on the further research on treatment of progeria too that will perhaps overlay its way towards the designing of a more definite and promising treatment strategies for this rare and complex syndrome.

CONCLUSION:

In the field of research, gerontology has also gained popularity off lately. Currently the researchers have also focussed towards delaying the normal aging phenomenon which has its own physical, psychological and social implications associated with it. Hence it is so essential to understand the molecular mechanisms which is responsible for aging as well as accelerate the aging process primarily the reason for progression of the disease.

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FIGURE:

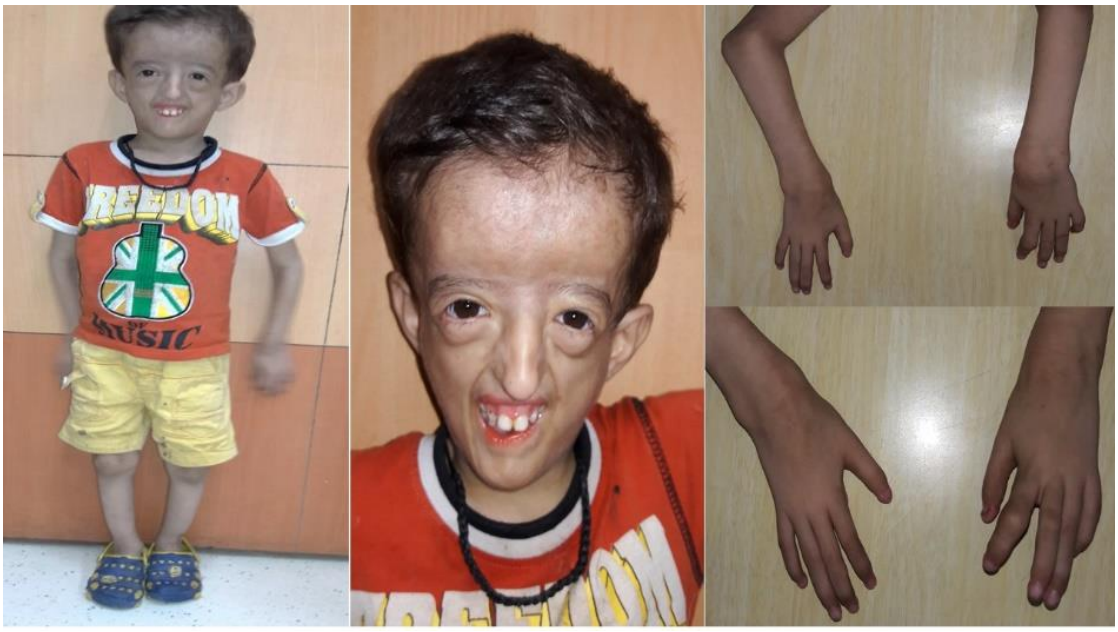


Figure 1: Extra oral photograph showing short stature, extra oral features, and deformity in extremity.

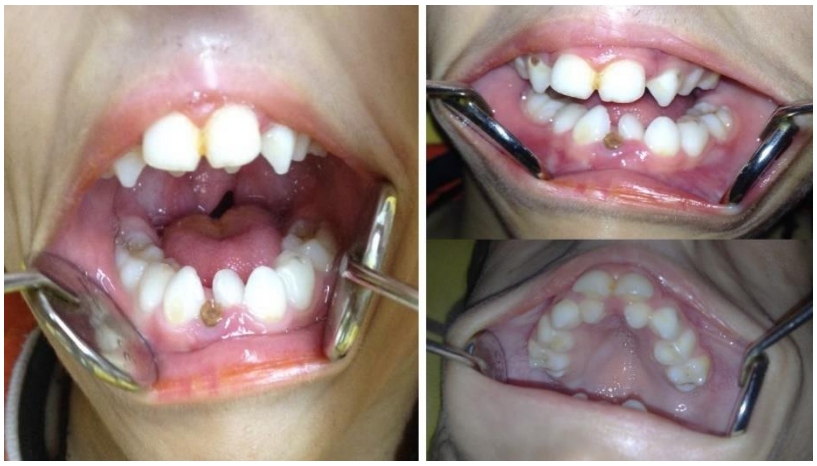


Figure 2: Intra oral photograph showing high arched palate, microglossia, few missing teeth.

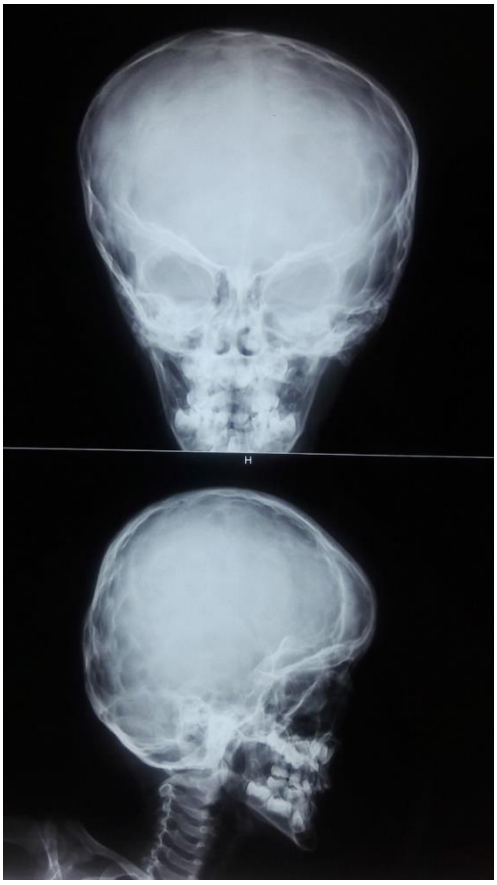


Figure 3: Skull radiograph showing brachycephalic head

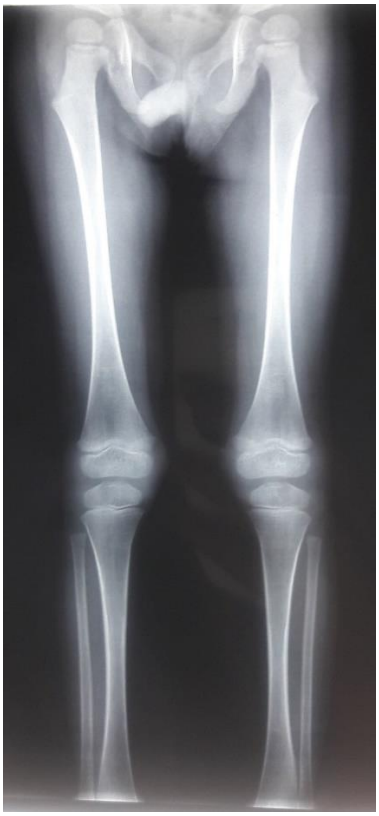


Figure 4: Lower limb radiograph showing displaced femur head, coxavalga deformity

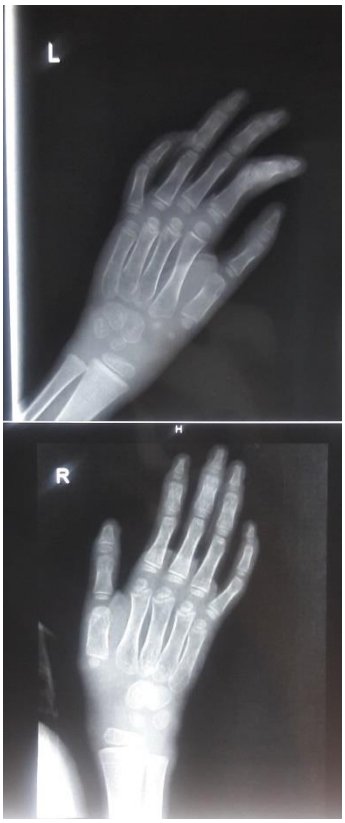
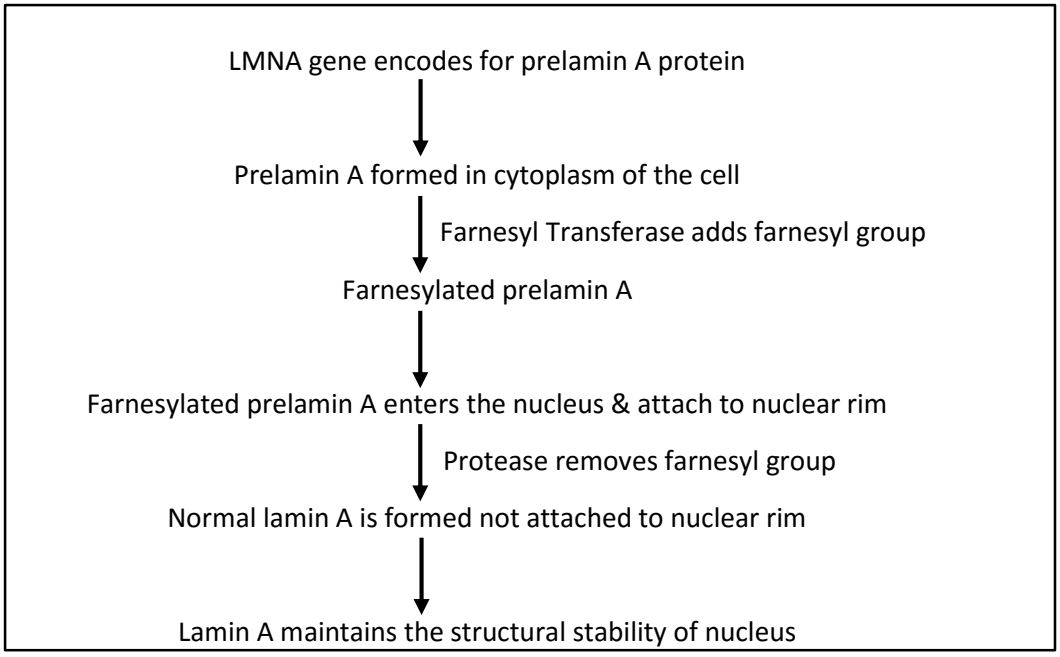


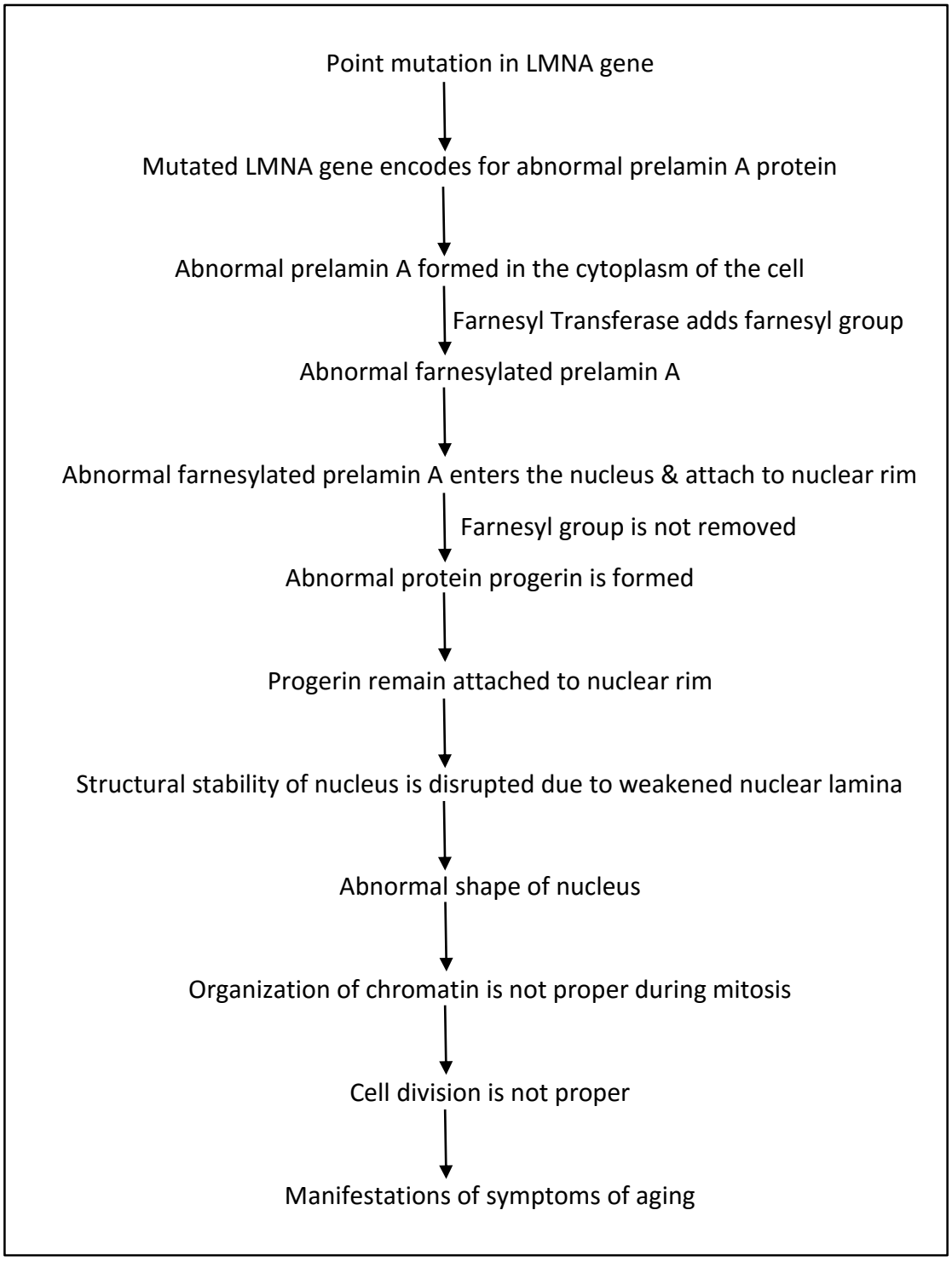
Figure 5: Hand radiograph showing discrepancy in carpal bone

CHARTS:

Flow Chart 1: Molecular sequence in a normal cell



Flow Chart 2: Molecular sequence in a cell in progeria



TABLES:

Table 1: Table showing various progeroid syndromes

Defect	Syndrome	Clinical Features
Defect in DNA repair	Werner Syndrome	Adult progeria, Symptoms appear mostly during teenage, cataract, atherosclerosis, skin atrophy, osteoporosis, etc.
	Bloom Syndrome	Short stature, facial rash due to telangiectasia, small head & face, café-au-lait spots, photosensitivity, abnormal immune system, pneumonia, middle ear infection, hypogonadism, increased risk of developing few malignancies, etc.
	Rothmund-Thomson Syndrome	Small stature, sparse hairs, eyebrows, cataract, abnormal dentition, osteopenia, gastrointestinal problem, increased risk of developing few malignancies, etc.
	Cockayne Syndrome	Growth failure, atypical photosensitivity, impaired nervous system development, poor cognitive skills, loss of hearing & vision, etc.
	Xeroderma Pigmentosum	Symptoms appear at 6 months, first stage by diffuse erythema, scaling, freckles over light exposed areas, second stage by poikiloderma which is skin atrophy, telangiectasias, mottled hyper & hypopigmentation, third stage by numerous malignancies such as malignant melanoma, basal cell carcinoma, squamous cell carcinoma & Ocular problems, etc.
	Trichothiodystrophy or Tay's Syndrome	Growth & mental retardation, congenital icthyosiform eryhthroderma, brittle hair, etc.
Defect in Lamin A/C	Hutchinson Gilford Progeria Syndrome	Growth retardation evident within one year of birth, skin atrophy, alopecia, osteolysis, cardiovascular complications, etc.
	Li-Fraumeni Syndrome	Breast cancer, neurological involvement including seizures, headache, abnormal gait, brain cancer, soft tissue & bone sarcoma, acute leukaemia, prepubertal genital hair, deep voice, adrenal cortical carcinoma, etc.
	Rapadilino Syndrome	Slow growth, short stature, underdeveloped or absent patellae, cleft palate, dislocated joints, diarrhoea, vomiting, etc.
	Baller Gerold Syndrome	Symptoms overlap with Rothmund Thomson Syndrome & Rapadilino Syndrome.
	DeSanctis Cacchione Syndrome	Combination of xeroderma pigmentosum & neurologic abnormalities
	Nijmegen Breakage Syndrome	Short stature, immunodeficiency, radiation sensitivity, increased risk of lymphoid malignancies, etc.
Other Related Disorders	Dyskeratosis Congenita	Nail dystrophy, abnormal skin pigmentation, mucosal leukoplakia & pulmonary complications, etc.
	Fanconi Anemia	Bone marrow failure, pancytopenia, predisposition to malignancies, short stature, microcephaly, café-au-lait spots, etc.
	Ataxia Telengiectasia	Cerebellar ataxia, decreased mental development, discoloration of sun exposed skin areas, café-au-lait spots, enlarged blood vessels, nystagmus, premature hair graying, radiation sensitivity, severe respiratory infections, etc.
	De Barsy Syndrome	Skin is lax, wrinkled, sagging, lacks elasticity, eye abnormalities, growth abnormalities, prematurely aged appearance, etc.
	PIBI(D)S Syndrome	Photosensitivity (P), ichthyosis (I), brittle hair (B), impaired intelligence (I), possible decreased fertility (D), short stature (S)