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A BRIEF REVIEW ON HUTCHINSON-GILFORD PROGERIA SYNDROME

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Abstarct:

Hutchinson-Gilford Progeria Syndrome (HGPS) was first documented in 1886 in the medical literature. A HGPS patient has the physical characteristics and appearances of an elderly individual. It is now clear that the syndrome results from the accumulation of a metabolite formed during processing of the mutated pre-lamin A protein. The purpose of this review is to increase the awareness of Hutchinson-Gilford Progeria Syndrome and its conditions and discuss the new therapeutic approaches among worldwide.

Key words: *Hutchinson-Gilford Progeria Syndrome, bone deformation, pre-lamin A, Progeroid syndromes.*

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INTRODUCTION:

Progeroid syndromes (PSs) are a gaggle of fatal, severe and rare genetic disorders characterised by different clinical options and phenotypes of physiological ageing untimely. These syndromes embrace clinically and genetically heterogeneous diseases like ataxia-telangiectasia, Bloom syndrome, Cockayne syndrome, Fanconi anaemia, Hutchinson-Gilford syndrome, Rothmund-Thomson syndrome, trichothiodystrophy, xeroderma pigmentosum, and Werner syndrome (also called adult progeria)[1]. Among the various varieties of abnormality, the classical and most extensively studied kind is that the Hutchinson–Gilford syndrome (HGPS), named when the 2 scientists (Jonathan hutchinson in 1886 and Hastings Gilford in 1897) WHO severally depicted and delineate the syndrome. Hutchinson–Gilford progeria syndrome (HGPS) could be a rare genetic disease that's characterised by dramatic premature aging and accelerated cardiac disorders.

This syndrome was initially described over one hundred twenty years ago by Hutchinson [2], and although the phenotype includes some aging-like changes, biogerontologists have questioned whether or not it's a viable model for finding out accelerated aging [3]. The question has again risen up with the recent identification of LMNA as the gene responsible for this sporadic autosomal dominant syndrome [4].In addition to progressive atherosclerosis disease, HGPS is characterised by bone deformations, as well as craniofacial disproportion, jaw and clavicular hypoplasia, and osteoporosis, similarly as by a loss of s.c. fat, delayed dentition, sclerodermatous skin, joint stiffness, and hip dislocations [5, 6, 7]. The different parameters like somatotropic hormone, thyroid and parathyroid functions, pituitary and adrenal glands are found to be normal whereas there could also be accelerated metabolic rate. A very low degree of insulin resistance has been reported in some cases. Abnormality in skin could also be attributed to elevated elastin and collagen IV production [8]. Scientists are significantly interested in Progeria abnormality because it would possibly reveal the clues about normal ageing method [9, 10].

HISTORY

Hutchinson-Gilford Progeria Syndrome (HGPS) could be a terribly rare illness, rumored to occur in one in eight million newborns. Below one hundred fifty cases were reported within the scientific

literatures since condition is very rare [8]. At cellular and molecular level, HGPS is characterised by severe alterations of the nuclear design, chromatin organization, epigenetics and regulation of transcription. Apparently, the changes determined in HGPS were typically the same as those determined within the elders [8, 9].

A few decade ago at a nonscientific venue: a party in Washington, D.C. throughout the event, the genomic scientist among us (Collins) happened to strike up a voice communication with a young hospital room physician (Scott Berns) doing a White House Fellowship. The ER doctor mentioned that he and his physician-scientist married woman had a young son with HGPS, that could be a rare disease characterised by speedy, premature aging[10]. The molecular reason for HGPS was unknown at the time, creating the hunt for potential treatments and cures virtually not possible. Berns told Collins that the couple had supported for the abnormality analysis .Foundation also encourage scientists to do work on this formidable challenge. After a number of additional conversations, the genomic scientist was “hooked,” and in agreement to assist, organize a workshop to assist hunt down the change liable for HGPS. Pretty also his laboratory joined in. But some elements were more crucial, perhaps essential, to motivating basic scientists to use their work toward clinical issues. Among the foremost is need of human. Within the case of HGPS, the requirement was obvious: there was no treatment for this illness, and patients died from disorder at around age thirteen.

Another key incentive is intellectual challenge. Nature could cause a lot of harder analysis queries than we are able to create by mental act ourselves, as we've learned time and time once more in our decade of learning HGPS. We have a tendency to motivating force of technological innovation. Clinical issues once thought-

about too tough or time overwhelming to be tackled by basic analysis will become amenable to answer because of the event of latest tools and technologies. Within the genomic sector, such innovation includes databases containing the reference sequence of the human genome, maps of human genetic variation, and ever expanding catalogs of human genotype/phenotype correlations. Refueling this sudden innovation in genomic discovery technology that have dramatically cut the value of deoxyribonucleic acid sequencing from $100 million per genome in 2001 to < $8,000 today. Cell biology, too, has benefitted greatly from technological advances over the past decade. These advances are, the spinning disk and other advanced confocal microscopes that, beside higher speed cameras, create it attainable to record 3D pictures in living cells over long periods of time[11]. By these techniques of photobleaching and photoactivation, new fluorophores with a large range of excitation wavelengths have additionally provided extratools to label and track however proteins behave in living cells[12,13]. For better imaging tools, cell biologists currently have access to several additional wet-bench biochemical assays and kits for determining numerous cellular processes, together with cell death, senescence, phosphorylation, adenosine triphosphate production, and cell stress. These kinds of tools are essential for dissecting out the molecular mechanisms underlying HGPS.

ETIOLOGY

Most scientists and researchers have determined that random mutations cause Hutchinson-Gilford abnormality syndrome. These mutations are either inheritable through autosomal dominant traits or occur by complete random change in chromosome 1[14]. This chromosome is referred to as LMNA that codes for the lamin A and lamin C proteins. Usually, lamin A proteins give support to the nuclear membrane. The mutation of the gene, found in HGPS patients, is that the replacement of a cytosine with a thiamine ester at a particular position on the chromosome sequence (position 1824, written as C1824T). The mutation, referred to as G608G, causes production of abnormal prelamin A's, referred to as progerins, that may become lamin A protiens. These abnormal proteins an area unit missing fifty amino acids on one finish and can't properly support the nuclei walls. This mutation, however, doesn't have an effect on lamin C proteins. Scientists believe that this mutation and also the unstable nuclear membranes made might cause the premature aging related to HGPS. In elder humans, the nuclei of cells are equally misshapen. This connection results in the understanding of the similar characteristics found in HGPS patients and non-affected human elders.[15]

SIGNS AND SYMPTOMS

Hutchinson–Gilford abnormality syndrome (HGPS) is an especially rare and uniformly fatal ''premature aging'' unwellness during which all kids die as a consequence of MI or Cerebrovascular accident at a mean age of twelve years (range, 8–21 years). The earliest manifestations of the unwellness are seen at _12–14 months and shows alopecia and growth retardation (Progeria Research Foundation's medical and research database).Additionally to progressive coronary-artery disease, HGPS is characterised by bone deformations, together with craniofacial disparity, mandibular and clavicular hypoplasia, and osteoprosis, also as by a loss of s.c. fat, delayed dentition, sclerodermatous skin, joint stiffness, and hip dislocations [15-16].

A number of physical characteristics of HGPS includes loss of hair together with scalp and eyebrows, outstanding scalp veins and forehead, classical face expression together with frontal bossing, sticking out ears with absent lobes, a glyphic broad, gently bursiform nasal ridge nose, outstanding eyes, thin lips and micrognathia (small jaw) with a vertical midline groove within the chin[16,17,18]. Abnormal and delayed dentition is common, and skinny and infrequently tight skin results from important loss of s.c fat [19]. HGPS patients have high-pitched voices, a horse-riding stance, restricted joint mobility and have short stature median final height of 100-110cm, median final weight of 10-15Kg. As they mature, they develop osteolysis, notably involving the distal phalanges and clavicles. On average, death happens at the age of thirteen, with a minimum of ninetieth of HGPS subjects dying from progressive artherosclerosis of the coronary and cerebrovascular arteries. The earliest symptoms are failure to thrive and a localized scleroderma-like skin condition. As a toddler ages past infancy, further conditions become apparent.Growth retardation, alopecia, and a particular look (small face and jaw, pinched nose) are all characteristic of Progeria. The characteristic clinical finding of Hutchinson-Gilford abnormality syndrome (HGPS) includes abnormalities of the skin and hair additionally with characteristic facial features and skeletal abnormalities. Delayed, abnormal dentition is very common. Kids diagnosed with this disorder typically have tiny, fragile bodies, like those of old individuals. Later, the condition causes

wrinkled skin, coronary-artery diseases, and cardiac problems [20, 21].

PATHOPHYSIOLOGY

The main symptom in the patient with HGPS occurs because of mutation within the gene LMNA. The gene, LMNA, situated on band 1q21.1-1q21.3, encodes Lamin A, that may be a type V intermediate filament protein that localizes to the nucleus and forms the nuclear lamina within the nuclear membrane [22] . De novo mutations related to advanced paternal age are the cause of most cases. Lamin A and Lamin C, 2 abundant structural proteins of the nuclear lamina, are the products of an equivalent gene, LMNA. Lamin A is 12 exon protein. Prelamin A, the precursor of Lamin A, involves the joining from middle of coding DNA ten to coding DNA eleven then to coding DNA twelve [23].

Prelamin A has CAAX as terminal amino acids. This terminal triggers farnesylation of the carboxy terminal amino acid cysteine (the C of the CAAX tetrapeptide) by a cytosolic enzyme, called protein farnesyltransferase. The farnesylated Prelamin A attaches with the Endoplasmic Reticulum. After farnesylation, the last 3 amino acids of Prelamin A are cleaved by an endoprotease. The enzymes responsible for release of e amino acids are: Zn metalloprotein ZMPSTE24 and a prenyl protein endopeptidase RCE1 [24, 25]. After releasing terminal amino acids, farnesyl-cystein residue is methylated by Isoprenylcystein Carboxy methyl transferase enzyme (ICMT) [26, 27]. In the last step of Lamin A synthesis, last fifteen amino acids of Prelamin A including farnesylcystein methyl ester are released off by ZMPSTE24 and mature Lamin A is discharged from endoplasmic reticulum into cytoplasm..

The ensuing protein, Lamin A, isn't a longer membrane-bound one, and carries out functions within the nucleus [28, 29]. within the person there's mutation in one cistron of the LMNA gene. Roughly ninety percentage of patients with the syndrome have a uniform mutation in one cistron of the gene, consisting of a C-to-T substitution at nucleotide 1824 (1824 C→T). The disorder is rare as a result of affected individuals die before reproductive age, thus each case represents new mutation, and also the mutation must be exactly targeted to produce the new phenotype. The LMNA mutation at position 1824 doesn't modify the amino acid of the corresponding sequence within the messenger RNA (mRNA). However it causes defective informational RNA junction by activating a cryptic splice donor in coding DNA eleven, leading to a synthesis of abnormal macromolecule named "Progerin," with a deficiency of a hundred and fifty bases i.e. fifty amino acids as compared with traditional Lamin A. The defective splicing caused by 1824 C→T mutation deletes the part of protein that is targeted by ZMPSTE24 at the release step [30]. This leads the defective Progerin to stay farnesylated and membrane bound. The Progerin therefore formed enters the nucleus by diffusion through endoplasmic reticulum. The prolonged binding of Progerin to nuclear membrane disrupts the nuclear lamina inflicting blebbing of nuclear membrane that results in abnormal binding of chromatin granule to nuclear envelope . The relation of these sequence of reactions with clinical options of Hutchinson–Gilford abnormality syndrome in not terribly clearly understood . The abnormal nuclear membrane is susceptible to mechanical damage resulting in multiplied death. The disturbed binding of chromatin granule to nuclear membrane could cause abnormal gene expression. Similarly the defected nuclear lamina could have an effect on the conventional DNA repair mechanism [31].

A characteristic finding in persons with abnormality is a rise in hyaluronic acid excretion. Additionally to persons with abnormality, it's solely detected in those with Werner syndrome, a sickness characterised by a later onset of premature aging that happens throughout the second decade of life. Usually, hyaluronic acid and different glycosaminoglycan production will increase throughout the fifth to seventh decades of life. Possibly, the rise in hyaluronic acid may be a normal feature of advancing age. Fibroblasts from patients with abnormality show a 3-fold increase in total glycosaminoglycan production and, specially, hyaluronic acid production, compared with age-matched management groups. This increase results from an abnormality in degradation and isn't caused by its more synthesis. Hyaluronic acid is additionally necessary for the morphologic development of blood vessels. Absence of blood vessels is noted in regions of high hyaluronic acis levels. The less density of vasculature, sclerodermatous changes within the skin, and also the high prevalence of heart disorders may present in persons with Progeria is also elicited by high hyaluronic acidevels. More hyaluronic acid levels may additionally promote calcification of blood vessels, this leads to arteriosclerosis[32].

DIAGNOSIS

For locating a good treatment for HGPS remains on, nonetheless there's still no diagnostic kit offered for early detection of this disease. Sometimes in observe, a clinical assessment is completed, supported the constitution proof and anamnesis of the kid. Following this, a genetic check for LMNA mutation is often in deep trouble confirming the diagnosing of HGPS to initiate the treatment programmes early within the progression of the disorder. A case report on HGPS has rumored that clinical diagnosing also can be established by imaging findings - dislocation of the fibrous joint with many wormian bones within the skull; hypoplastic jawbone with infantile angle; the presence of fish-mouth vertebrae; the prevalence of bilateral spheroid joint valga deformity; biological process of terminal phalanges, etc. Finding of LMNA truncating mutation might even be useful within the diagnosing. Thinning and biological process of the distal clavicles is that the most consistent abnormality to be found within the thorax [33].

TREATMENT

Up to now, no effective medical aid is on the market for HGPS. The cardiovascular conditions are fastidiously monitored and therefore the use of low-dose aspirin may be a typically counseled medication. The employment of Farnesyl transferase Inhibitors (FTIs), similar to the lonafarnib, showed some restricted improvement within the conditions of the patients. Many medicine approaches are tried to ameliorate specific conditions (e.g. the zoledronic acid wont to increase bone mineral density).

Up to date, the sole treatment that has the aim to revert the causative agent of HGPS is that the FTIs treatment that tries to scale back the quantity of farnesylated progerin. Unluckily, FTIs treatments showed solely modest results [1, 13]. So as to seek out an efficient treatment for HGPS the chance of gene therapy is presently taken into consideration. The employment of the CRISPR/Cas factor gene editing system delivered by non-integrating viral vectors may be a remarkable approach for the genetic medical aid of HGPS [34, 35].

Kids may additionally benefit from a high-calorie diet. Human growth hormone treatment has been used. Researchers have known 2 further medicines that, once employed in combination with this FTI drug being tested, might give a good treatment for kids with abnormalcy than FTI's alone. These are Pravastatin drug and Zoledronic acid. Pravastatin drug may be a member of the drug category of statins. It's typically used for lowering cholesterol and preventing cardiac diseases. Zoledronic acid may be a bisphosphonate, typically used as a bone drug in oesteoporosis, and to forestall skeletal fractures in individuals tormented by some kinds of cancer. All of those 3 medicine block the assembly of farnesyl molecule that's required for Progerin to make sickness in Progeria[36,37].

The employment of this technology looks significantly suited to the treatment of genetic diseases caused by a dominant negative mutation, such within the case of HGPS. In detail, specific order of gene editing within the mutated locus will activate either NHEJ repair system, that may lead production of a truncated kind of progerin that extremely resembles the wild sort unfarnesylated mature lamin-A, or the HDR repair system used either the wild type allele factor as donor or a co-transfected donor plasmid, that may cause the production of wild type lamin-A. Whatever it'll be the case, the modifications are going to be permanent, and it'll be genetic by the daughter cells through the complete lineage. The primary evidences of the adenoviral-based CRISPR/Cas treatment in mammals are terribly promising, and that they appear to assure a high potency of order of gene editing with only a few off-target events [38-40].

Although there's no cure for HGPS, medical aid and medications are prescribed for patients to treat symptoms. Physical and occupational therapy are used to maintain a definite range of motion, and to comfort the muscles and bones. Certain exercises are used and any changes in body movements are recorded.

CONCLUSION:

Tremendous analysis has been tired this decade that has greatly increased our understanding of HGPS, however an enormous increase within the analysis into HGPS and therefore the study of persons with HGPS is named for and is far required. These studies can enable us to grasp if HGPS is nature's approach of presenting a rare and precious chance to examine the results of aging in a very dramatically accelerated fashion, and is permitting us to grasp the cellular mysteries of natural aging totally. It's hoped that this analysis can help the treatment modalities which can enhance the standard of life in people born with

HGPS. Because of the rarity of the sickness it becomes rather troublesome to hold out clinical analysis on the medicine. Presently Farnesyl transferase Inhibitors (FTIs) are the square measures being looked upon as potential drug treatment for this sickness. Lonafarnib is undergoing test|phase II clinical trial. Untill specific drug treatment is discovered, the appurtenant therapies like somatotropic hormone, Aspirins etc together with numerous measures to stop the complications of the sickness might prove helpful in prolonging the life to some extent.

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