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Review Article

Treatment Strategies for Toxic Protein Progerin: Hutchinson- Gilford Progeria Syndrome

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ABSTRACT

Hutchinson- Gilford Progeria Syndrome (HGPS; MIM 176670) is a rare fatal genetic disorder similar to a rapidly increasing age in symptoms. Aging is the main risk factor for heart diseases. It is becoming more prevalent in our societies. Hutchinson- Gilford Progeria Syndrome is an extremely infrequent inherited disease characterized by too early and fast aging immediately after being born. It a rare autosomal dominant genetic disorder, in 1 to 4 million births, for which there is no known cure. Children with HGPS succumb to myocardial infection and stroke in their teens and die of progressive vascular disease at an average age of 14 years. The average life of a child with HGPS is about 13 years. Some can die young with the disease and others may live longer, even for 20 years. The aim of this review is to understand the various aspects of disease special emphasis on pathophysiology, symptoms', and recent trends in medicine and future treatments. Different treatment strategies could be used for the treatment of HGPS including ATP- based therapy, MB treatment, CRISPR Cas9. Vascular calcification results by pyrophosphate deficiency in children with HGPS. The mechanisms involved in vascular calcification in children with HGPS analyzed by the researches on mouse. ATP-based therapy could be used as treatment strategy for this devastating disease and other pyrophosphate related diseases. As HGPS is caused by C to T mutation in 11 exon, LMNA gene instead of activating cryptic site leaves amino acid codes unchanged that result in deletion of amino acids. These changes involves in different mechanisms like mitosis aberration, altered chromatin organization, transcriptional organization that causes nuclear abnormalities. Mitochondria is very intense organelle that plays very important role in our body, it also acts as key element in aging. Abnormal mitochondria can cause many damages by increasing levels of reactive oxygen species and altering DNA and protein structures. Mitochondrial abnormalities also reported in HGPS fibroblasts along with depletion of ATP and altered levels of ROS. HGPS fibroblasts of mouse are treated with methylene blue (MB), an antioxidant that normalizes the mitochondrial abnormalities and aging phenotypes in mouse.

Key Words: HGPS; Progerin; Lamin A/C; Methylene blue; Early aging; Fibroblasts; CRISPR Cas9; Gene therapy

INTRODUCTION

Hutchinson- Guilford Progeria Syndrome is rare but a serious disease of premature aging; has existed as clinical body for about 100 years. HGPS is a destructive; aging; untreatable disease caused by the accumulation of protein that is toxin (lamin a) protein. HGPS has been established in an investigation with a characteristic; identification of the heterogeneous pathogenic variant in LMNA that produces the abnormal LMN A protein; which is Progerin [1-5].

LITERATURE REVIEW

HGPS is very rare disease present in only one birth out of four million births. At present there are only 36 to 46 cases of HGPS in the whole world. About 100 years ago it was first described by Dr. Jonathan Hutchinson; from that time only 100 cases have been observed around the world. English persons reported 97% cases of HGPS; this racial factor is still unknown. Generally this disease does not pass from parents to children because patients with HGPS die before reproducing. It is caused by the mutation in the early division in cells of children. It is genetically dominant disease that's why parents who are healthy will not pass it to their children. There are only two cases in which healthy parents passed it. In an Indian family; there are five children's of the same family suffering from this disease. In a Bengali family there are two children of the same family suffering from this disease [6-10].

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Clinical manifestations

Hutchinson-Guilford Progeria Syndrome (HGPS) can be identified by symptoms including early aging; failure to thrive in first few years after birth [11]. Physical appearance in not at all similar to normal persons as their heads are abnormally large for the face; thin vermillion of lower and upper mouth lip [8]; small mouth; subcutaneous fat loss; hearing loss; baldness; nail dystrophy; dental congestion. Mental and motor development is normal [8]. Death occurs as a result of complications of severe atherosclerosis; either heart disease or cardiovascular disease [11]; typically between the ages of six and 20 years [9]. The life span of persons with HGPS is round about 13 years some persons with HGPS die younger than it and some persons with it can survive about 20 years [2]. Hutchinson-Guilford Progeria Syndrome (HGPS) develops in individuals with severe growth failure; areas of sclerodermas skin; partial alopecia leading to total baldness by the age of two; generalized retrognathia; X-ray detections; includes distal clavicle and terminal pharyngeal restoration; and the establishment of general intellectual development delayed/incomplete primary tooth eruption. Lack of development, short stature, poor weight gain, loss of weight or height, reduced hypodermic low-fat [12-16].

DISCUSSION

Current treatments for HGPS

There is no effective treatment for HGPS. The cardiovascular activities are monitored on regular basis and a low amount of dosage of aspirin is the only medicine for HGPS in present. Farnesyl transferase inhibitors (FTI) such as tipifarnib and lonafarnib are the only drugs that showed a small amount of but limited improvement in the patient's health. This is the only treatment for removing the causative agents of HGPS; by inhibiting the fernesylated progerin. FTIs are currently used for the treatment of HGPS but unluckily it shows modest results only for the treatment of HGPS.

Hutchinson- Gilford Progeria syndrome is caused by the point mutation in the LMNA gene that protrudes as possible contender for gene therapy [17]. CRISPR Cas9 dependent treatments hold substantial guarantee for the treatment of genetic disorders. As HGPS is the dominant negative mutation in the LMNA gene that results in accumulation of lamin A which is toxic protein progerin [18,19]. Recent revolutions in genetic engineering are the production of CRISPR Cas9 tool for gene editing [19]. This tool is potentially great for genomic editing for gene therapy. It prevents the mutations by using viral vectors such as adeno- viral vectors etc. If the vectors cannot integrate within the host; then manipulates the genomes of the host. [18]. Genome editing with CRISPR Cas9 prevents the toxic protein progerin.

MB treatment

HGPS is a severe genetic disease responsible for early aging in children's [12]. For researches in HGPS; all reports had interest in nuclear phenotypes in HGPS [12]; but now we are focused on the mitochondrial functions that involves in normal aging and it is unclear in HGPS studies. Intense mitochondrial analysis showed increased fraction [20-22]; swollen mitochondria and reduction in mitochondrial mobility [13]. The expressions of normal protein are inhibited by toxic protein; progerin. For these mitochondria was treated with methylene blue along with HGPS cells. Methylene Blue treatment removed progerin from nuclear membrane and saved heterochromatin loss; corrected expressions of gene in cells [23,24]. So MB treatment can also be used for Hutchinson-Gilford Progeria Syndrome. Methylene blue is an antioxidant which can be used for the treatment of HGPS. Researches' have done on genetically modified mouse models [12]. In this two normal fibroblast lines and two HGPS- fibroblasts lines stained with Mito Tracker showing severe abnormalities in mitochondria and percentages of progerin lamin A/C have been observed [13]. Then both; normal fibroblast lines and HGPS fibroblast lines are treated with MB then RT-PCR analysis of fibroblasts takes place. After that western blotting; nuclear fractionation of both fibroblasts treated for about 6 weeks [12]. We found that MB treatment not only rescues mitochondrial defects but also removes HGPS assay mark nuclear blebbing [12,15]; makes better the heterochromatin organization and corrects the unregulated genes in the HGPS nucleus [12,15]. The advantageous effects of methylene blue treatment on HGPS are caused by dislocation of progerin from nuclear membrane to nucleoplasm [12]. The final results showing the expression of down-regulated genes; unaffected genes and up- regulated genes [13]. The ratio of unaffected genes is more which is showing that MB treatment works; showing that how MB treatment worked with HGPS nucleus and improved the nuclear shape; restoration of heterochromatin loss; corrected gene expression [13]. And also showing that how MB treatment worked with abnormal destructive mitochondria by lowering levels of ROS and increasing ATP levels [12,13]. From this; it is shown that MB treatment can also be used for treatment of children with HGPS.

ATP Based Therapy can also be used for the treatment of Hutchinson Gilford Progeria syndrome [23]. Researchers have found by experiments in mouse that ATP based therapy prevents vascular calcification and can extend the lifespan of a mouse with HGPS; MIM 176670 [23]. Pyrophosphate deficiency explains the excessive vascular calcification found in children with Hutchinson–Gilford progeria syndrome (HGPS) and in a mouse model of this disease. In HGPS; pyrophosphate synthesis from ATP reduced and pyrophosphate hydrolysis increased. The reduced production of pyrophosphate along with decreased levels in plasma ATP; results in reduced plasma pyrophosphate [23]. In this therapy; two inhibitors were used levamisole and ARL67156 increased the synthesis and lowers the degradation of pyrophosphate; in mouse with HGPS. These inhibitors provide therapeutic approach for this devastating disease [23]. Treatment of mouse with ATP prevented vascular calcification but not increased the life span of the mouse. But the treatment of mouse with ATP; levamisole and ARL67156 not only prevented the toxic protein but also increased the life span of the mouse [24-27].

CONCLUSION

The first treatment strategy for HGPS was based on farnesyl transferees' inhibitors (FTIs) to reverse the nuclear phenotype. Prelamin A and progerin alternatively undergo prenylation by geranylgeranyl transferees' when pharyngeal transferee's activity is inhibited. For this reason; an alternative treatment strategy used a combination of stains and bisphosphonates; inhibitors of HMG-COA reeducates; and farnesyl-PP synthase; to efficiently inhibit both farnesylation and geranylgeranylization of progerin and prelamin

A/C; which improved the aging-like phenotype of progeroid mice; including weight loss and prolonged reductions. These treatments showed reduced efficiency in children with HGPS. The next HGPS treatment strategy was based on retrogression of the HGPS mutation using CRISP-Cas9; which extended longevity in HGPS mice. However; this treatment is still far from being applicable in humans. Treatment of HGPS with methylene blue can work better. The combined treatment of ATP along with inhibitors and levamisole and ARL67156 prevents the production of toxic protein and increased the life span of mouse with HGPS. The ATP based therapy represents here is another strategy for the treatment of HGPS. This study also showed that the eNPP/eNTPD activity ratio plays an important role in pyrophosphate availability; as this ratio could determine the ratio of pyrophosphate/phosphate synthesis from ATP. ATP replacement therapy; combined with inhibitors; may provide an alternative to replacement therapy in patients with HGPS or other diseases with pyrophosphate deficiency.

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