International Research Journal of Engineering and Management Studies (IRJEMS)
Volume: 03 Issue: 04 | April -2019 ISSN: 1847-9790 || p-ISSN: 2395-0126

HUTCHINSON-GILFORD PROGERIA SYNDROME – A BRIEF REVIEW

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Abstract: *This paper provides the overview of Hutchinson-Gilford Progeria Syndrome (HGPS). It briefs about the relevance of the disease, latest research in the treatment strategies, major drawbacks in finding an ultimate cure and future perspective on the disease.*

Keywords: HGPS, latest research, drawbacks, therapeutic approach.

1. INTRODUCTION

Hutchinson-Gilford Progeria Syndrome (HGPS) commonly known as Progeria, belonging to the group of condition called laminopathies, is an extremely rare (occurring 1 in 4-8 million live births with male: female ratio of 1.5:1 having male dominance), autosomal dominant disorder which affects mostly during the childhood with astounding features resembling premature and accelerated aging in patients causing death usually due to cardiovascular complications at the mean age of 14.6 years. HGPS occurs as a heterozygous de novo point mutation (c.1824C>T, p.G608G) (NM_170707.3) located within exon 11 of the gene LMNA or lamin A which encodes the intermediate filament proteins lamin A and C, the structural components of the nuclear lamina. This mutation causes the production of a truncated toxic form of lamin A, formed due to aberrant mis-splicing which is called progerin. This progerin which is a dysfunctional protein accumulates on the nuclear rim, disintegrates structural support of nuclear lamina and disorganizes nuclear processes like DNA and RNA synthesis.

Clinical features of HGPS based on various parameters include: micrognathia, craniofacial disproportion, alopecia, prominent eyes, scalp veins, loss of body fat, slowed growth, scleroderma, macrocephaly, thin lips, high pitched voice, delayed and abnormal tooth formation, stiff joints, hip dislocation, insulin resistance, irregular heartbeat etc.

2. Latest research in the treatment strategies of HGPS

As per the latest research in HGPS, clinical reports by Leslie Gordon *et al.* (2018) demonstrated that Lonafarnib, a farnesyl transferase inhibitor (FTI), has been successful in promoting weight gain and improving cardiovascular and skeletal abnormalities in progeroid children thus extending their rates of survival. FTIs are the drugs that block the enzyme responsible for the farnesylation step in the synthesis of lamin A from prelamin A in Progeria. The inhibition of this step precludes the buildup of abnormal protein Progerin on the nuclear rim averting further progression of the disease. Recently, Sulforaphane (SFN), an antioxidant derived from cruciferous vegetables, has been described to enhance progerin clearance by autophagy and reverse the cellular hallmarks of HGPS *in vitro* by D. Gabriel *et al.* (2014). In May 2018, Dr. AlSogair's presentation, titled "Anti-Aging Potentials of Methylene Blue for Human Skin Longevity", provided compelling evidence of Methylene blue's ability to delay aging-related mitochondrial dysfunction and stimulate collagen and elastin.

Methylene blue actually reversed aging and showed promise in the treatment of Progeria. In April 2018, scientists from the University of Cambridge identified a potential therapeutic target in the treatment of HGPS. In a paper published in Nature Communications, scientists provided preclinical data showing that chemical inhibition or genetic deregulation of the enzyme N- acetyltransferase10 (NAT10) leads to significant health and lifespan gains in a mouse model for HGPS. By screening candidate molecules for an effect on nuclear membranes in human HGPS patient-derived cells *in vitro*, the authors had previously identified a smaller molecule called *remodelin* as an effective ameliorative agent. The results showed that the approaches significantly improved the health of the mice diseased with HGPS, increased their lifespan, and reduced the effects of the HGPS mutation across a variety of measures in body tissues and at the cellular level. In March 2018, a paper published in Cell Report, Saint Louis University researchers had revealed that replication stress is a key cause of the underlying DNA damage accumulation found in the cells of those suffering from HGPS. They demonstrated that progerin elicits replication stress and nuclease-mediated degradation of newly replicated DNA and it activates an interferon pathway. They found out that vitamin D reduces significantly the toxicity of progerin in cells from HGPS kids.

3. Drawbacks of the treatment approaches

Recent advances in the research on HGPS have led to the discovery of a large number of promising therapeutic candidates which may assist in the prevention of the advancement of this devastating disease. Nevertheless, the drawbacks of most of these approaches are that they lack sufficient *in vitro* and *in vivo* preclinical data to be ready for human application. A major limitation in the amelioration of Progeria arises from the fact that research is performed on the primary cultures of either patient's cells or animal models due to the finite supply of pathological samples from HGPS patients. In one study, elevation of the component hyaluronic acid, which normally increases with advancing age, has been demonstrated; but whether this elevation is of significance in the treatment of HGPS still remains to be proved. Also, various clinical trials have demonstrated that there are lesser benefits of FTI therapies and they do not help in the complete cure of the disease. Therefore, there is an urgent need for more treatment options to help people suffering from this debilitating disease.

4. Future perspectives on HGPS

The field of gerontology gained momentum comparatively late when compared to other areas of research. Hutchinson-Gilford Progeria Syndrome is a disease which has been a subject of curiosity among the scientists. This is because there are two important reasons. First, progress in HGPS can be viewed as a paradigm of modern translational medicine and second, discoveries in rare diseases often offer new possibilities for an understanding of cellular and organismal mechanisms, such as normal aging and cardiovascular diseases in the case of HGPS. (Gordon *et al.* 2014). Recent studies have shown the involvement of microRNAs and in particular, mir-9 which prevents progerin accumulation in HGPS neurons. Therefore, another possibility for developing new therapeutic approaches for progeria would be the modulation of microRNAs, taking into consideration off-targets that must be evaluated *in vitro* and *in vivo* before transposition to humans. (K. Harhouri *et al.* 2018)

As a future therapeutic approach that still remains to be evaluated for HGPS is the Clustered Regularly Interspaced Short Palindromic Repeats/Cas protein (CRISPR/Cas) for *in vivo* gene editing and repair of the disease-causing mutation. Also, Adeno-Associated Virus (AAVs) have gained popularity, in the last years, as safe gene delivery vectors, due to their ability to mediate long-term expression in both non-dividing and dividing cells, with specific tissue tropism. In this regard, AAVs constitute interesting CRISPR/Cas9 delivery candidates to specifically repair the progeria-causing mutation (K. Harhouri *et al.* 2018).

CONCLUSION

Though there has been a lot of advancement in the research for the treatment, the development of a truly creative therapy for HGPS remains elusive.

Also, why this disease affects the males more than the females and why ninety-seven percent of the affected patients are white are the questions which still remain unanswered. As of now, there is no FDA-approved drug that can provide a complete cure for patients with progeria; therefore, there is an urgent need in the scientific community to develop therapies for patients with this life-threatening disease. A better understanding of the causes of this syndrome might lead to better insights into the mechanisms of development as well as aging. Also, the coming era would prove exciting for the research in HGPS as the scientific community is united by a common goal: to find a magic bullet! As also said, "With research, the possibilities are limitless" we are close to finding the cure.

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