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Review Article

AN OVERVIEW OF PROGERIA: RARE DISEASE OF INDIA

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Abstract

Rare diseases (RDs) are conditions that affect a small percentage of the population and are often chronic and life-threatening. With more than 350 million people worldwide suffering from over 8,000 RDs, progeria stands out as a rare genetic disorder causing premature aging. This disorder includes syndromes like Werner syndrome, Bloom syndrome, Rothmund-Thomson syndrome, Hutchinson-Gilford syndrome (HGPS), and others, with HGPS being the most studied. HGPS is linked to mutations in the LMNA gene, which codes for lamin A and lamin C proteins. HGPS is caused by mutations in the LMNA gene, resulting in the production of an abnormal protein called progerin, which destabilizes cells and accelerates aging associated with detrimental phenotypic features. Progerin accumulation leads to genomic instability, dysregulated gene expression, delibated nuclear morphology and deficits in DNA repair. Awareness and education about rare diseases like progeria are crucial. Collaborative efforts involving patients, advocates, healthcare professionals, researchers, the pharmaceutical industry, and the government are essential for advancing research and treatment. Additionally, the potential role of nutraceuticals in future therapies should not be overlooked. Based on the articles analyzed, etiology, prevalence in India, treatment and supportive therapies and limitations of the reported treatment regimens have been examined. Possible targets identification, strategies for clinical trials are avenues for future research prospects.

Keywords: Werner Syndrom - Hutchinson-Gilford syndrome (HGPS) - LMNA gene – Lonafarnib – Farnesylation - Healthcare Professionals

1. Introduction

A population is when occasionally affected by a disease or a disease that affects a low percentage of population than other disease, that disease is termed as rare disease (RD). Though there is no any particular definition of RDs, there are so many quantitative and qualitative criteria to define it. Rare diseases are often chronic and life-threatening. More than 350 million people worldwide are affected by the rare disease and the number of RDs are more than 8000[1-3].

Progeria is a rare genetic premature ageing disorder. These syndromes comprise diseases such as Werner syndrome (adult progeria), Bloom syndrome (Bloom-Torre-Machacek syndrome), Rothmund-Thomson syndrome, Hutchinson-Gilford syndrome, Fanconi anemia, and ataxia- telangiectasia and Cockayne syndrome. Among them Hutchinson-Gilford syndrome or Hutchinson–Gilford progeroid syndrome (HGPS) is classical and most studied[4]. Progeriais linked with a subset of specific mutations in the LMNA gene, coding for lamin A and lamin C proteins[5].

Figure 1: Fifteen-year-old patient who died in 2016 was instrumental in creating awareness about the disorder in India

(Source: Bhushan Koyande/ Hindustan Times file photo)

2. History

The Greek word "próorageraséménos" means "prematurely old" and it is believed that the word "Progeria" is derived from the very Greek Word. In 1886, Dr. Jonathan Hutchinson first described the disease in 1886 and later in 1897, Dr. Hastings Gilford and therefore, the disease named as HGPS[6]. The author had described the first ever case in 1886 to be of a boy who had the appearance of an elderly person, with his limbs, fingers and nails with extremely thin and delicate features and a backward curvature. His skin was thin and sensitive, making his veins more visible than usual. Furthermore, he possessed almost no subcutaneous or adipose tissue. Gilford recognised details and characteristics to be "premature aging". After these cases, no cases of progeria were reported until 1910, when a 15-year-old French girl and a 27-year-old Dutch man were reported. Since then, the number of cases gradually elevated in all the continents, so that in 1972 there were 60 cases worldwide and until 2006 the number of cases reported touched 142[7].

3. Incidence in India

On December 2023, a report was published of a 14 years old boy from Madhya Pradesh who was detected as variant of progeria. It was perhaps the first case of Mandibuloacral Dysplasia B[8]. In 2016, as per Progeria Research Foundation (PRF), there were 7 reported and 66 unreported cases of HGPS[9]. In India, recent reports include the first case of Mandibulofacial Dysplasia B. Only 161 children are registered with The Progeria Research Foundation as of September 2019, despite specialists' estimate that there are 350–400 children with progeria living in the globe today. As a result, about 200 are still unidentified. Sixty of the unidentified children, or around 1/3rd of the total, are estimated to be untreated and in need of assistance in India. 18 children have been recognized in India over the past ten years. So that PRF can give these children the specialized care they require, residents of India can assist in locating additional Indian youngsters who suffer from progeria[10].

4. Symptoms

Symptoms of progeria cause a distinctive appearance. They are discussed below.

4.1 Arthritis Postnatal growth restrictions

Postnatal growth restriction refers to a condition where a newborn or infant experiences inadequate growth and fails to attain the expected growth milestones for their age. It is a symbol of insufficient nutrients delivery and insufficient protein-calorie availability that is needed for the fast growing newborn[11]. Restrictions in growth and poor weight gain, with below-average height and weight are the basic symptoms.

4.2 Midface hypoplasia

In midface hypoplasia upper jaw, cheekbones and eye sockets have not grown as much as the rest of the face, along with abnormal anterior positioning of the infraorbital and perialar regions and facial convexity is increased or the nasolabial angle is increased. It is also can described as underdeveloped midface[12].

4.3 Micrognathia

Micrognathia is nothing but underdeveloped jaw, when the mandible is smaller than normal. A case was reported recently in 2023 that an infant was diagnosed as HGPS with congenital micrognathia and upper airway obstruction caused by a novel LMNA mutationin Beijing Children's Hospital[13].

4.3 Osteoporosis

Osteoporosis is a bone disorder due to low bone mineral density (BMD), impaired bone mineralization and decreased bone strength[14]. Several case reports revealed that patient with HGPS had confirmed generalized and marked osteoporosis through the radiography. HGPS associated with severe osteolysis of the acra, clavicles, mandible and viscerocranium was reported[15].

4.4 Lipodystrophy

HGPS affected patient develop lipodystrophy caused by the absence or loss of subcutaneous fatalong with other normal features of ageing[16].

4.5 Miscellaneous

Along with above mentioned symptoms, some other significant symptoms were observed like low body weight, decreased joint mobility, alopecia.

4.6 Etiology

The LMNA gene produce two major proteins called laminA and lamin C that are made in most of the body's cell. The mutated LMNA gene and/or abnormal post-translational processing (ZMPSTE24 gene mutations) both of which ultimately result in abnormally formed laminA called progerin. Progerin makes cells unstable and appears to lead to progeria's aging process. De novo point mutations in the lamin A/C gene called LMNA (which produces lamin A and lamin C proteins as alternative splice products) causes HGPS [17,18].

5.Treatment

5.1 Lonafarnib

Lonafarnib is a farnesyltransferase inhibitor. The US Food and Drug Administration approved Zokinvy (lonafarnib) in November 2020 to treat the patients of HGPS[19]. Lonafarnib is used to reduce the risk of death in children 1 year of age or older with HGPS. reversibly binds to the farnesyltransferase CAAX binding site, thereby inhibiting progerin farnesylation and subsequent intercalation into the nuclear membrane[20].

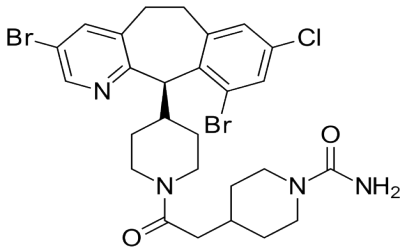

Figure 2: Structure of *Lonafarnib*

5.2 Rapamycin

Rapamycin, also known as "Sirolimus". Rapamycin is used to block the growth of structural defect in the nucleus and enhance the lifespan of affected cells. It also inhibits the atherosclerosis. Rapamycin can be administered to progeria patient because it needs blood draws to determine the levels of drugs. While FTIs may prevent the progerin from growth whereas injurious progerin is evacuated from cell by the rapamycin action[21-22].

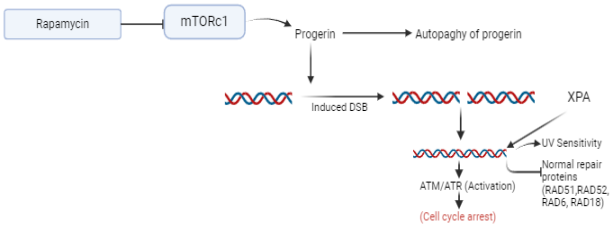

Figure 3: Mechanism of action of rapamycin against progeria

(Source: https://www.researchgate.net/figure/Mechanism-of-action-of-rapamycin-against- progeria 29 Jul 2024)

6. Supportive therapies Hydrotherapy

Hydrotherapy promotes relaxation, relieves pain, facilitates movement, and facilitates exercise. It can also help prevent the progression of arthritis[23].

6.1 Vitamin E

Vitamin E is a fat-soluble vitamin that protects Vitamin A and essential fatty acids from oxidation and prevents the breakdown of body tissues[24].

Vitamin E is an antioxidant that works to shield cells from the destructive effects of free radicals, which are waste products from the body's metabolism. Because free radicals can damage cells, they may play a role in the emergence of cancer and cardiovascular disease[25].

6.2 Aspirin

Aspirin nowadays used as a prevention of heart disease and reduce the risk of heart strokes and heart attacks.

6.3 Fluoride

Teeth issues are common in children. Teeth might be tiny, unevenly shaped, or even absent due to underdevelopment of the lower jaw and face bones, and tooth decay is a common occurrence.

Fluoride fortifies tooth enamel, increasing its resistance to dental decay, which is one of the main ways it can benefit dental health[26].

7. Conclusion

In any kind of rare diseases, awareness is an important issue. Not only the patients who are suffering but also society can take the responsibility to aware the people, and we have an example; there is a Hindi movie that tells the story of a 12 years old boy suffering from progeria. The awareness can be a successful event when patients, patient advocates, pharmacist and health care professionals, researchers, pharmaceutical industry, and government will be together. Future research to alleviate HGPS should be the interest for the young researchers and the role of nutraceuticals can't be ignored.

8. Conflict of Interest: None

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