PROTEUS SYNDROME: NEED FOR PATIENT CENTRIC DRUG DELIVERY

Nikhitha K Shanmukhan\textsuperscript{a}, Arun Radhakrishnan\textsuperscript{a}, Prineetha M\textsuperscript{a}, Anusha S\textsuperscript{a}, Aravind K\textsuperscript{a},
Chinnapaiyan A\textsuperscript{a}, Bolisetty Kasi Viawanath\textsuperscript{a}

\textsuperscript{b}Department of Pharmaceutics, JSS College of Pharmacy, Udagamund, JSS Academy of Higher Education and Research, Mysuru, India.

*Corresponding Author:
Arun Radhakrishnan
Department of Pharmaceutics,
JSS College of Pharmacy, Udagamund,
JSS Academy of Higher Education and Research, Mysuru, India.
Email: arunpharma93@gmail.com
Phone: 7402222019
ABSTRACT

Proteus syndrome is a hamartomatous disorder with multisystem involvement results from mutation in AKT1 gene. Since the symptoms and severity of Proteus syndrome are unique to each patient, diagnosis and treatment become hard to the physician. This article is concentrated on the identification and recognition of specific characteristics of the disease, pathophysiology, symptoms, diagnosis, treatment and necessity of advanced diagnosis, effective generalized and personalized therapy as well as the requirement of new drugs for the management of Proteus syndrome. Detailed studies on Proteus syndrome and the evidences from the case reports revealed the requirement of intense care, diagnosis and an effective treatment for each patient preferably patient centric drug delivery due to the high degree variation in the symptoms and clinical features among patients.

Key Words: Proteus syndrome, AKT1 gene, pathophysiology, symptoms, diagnosis, generalized and personalized treatment.

1. INTRODUCTION

Proteus syndrome is a hamartomatous disorder with multisystem involvement results in excessive growth of body parts asymmetrically with high clinical variability resulted from mosaic mutation in of AKT1 gene [1]. Affected individuals experience complications such as skeletal malformations, benign and malignant tumors, malformations of blood vessels, bullous pulmonary disease, and certain skin lesions in some people, life-threatening conditions relating to abnormal blood clotting may develop including deep vein thrombosis and pulmonary embolism [2]. Proteus syndrome stay silent in newborns and exhibit the symptoms within 6-18 months and becomes severe with age. Particular cells effected from mutation produces abnormal protein that increases
the cell proliferation and the unaffected cells behave normally. Since the disease is rare and the
diagnosis is difficult due to the high variability in symptoms creates difficulty in early diagnosis
and treatment [3].

2. EPIDEMIOLOGY

Proteus syndrome is very rare with less than 100 individuals conformed affected. 1 case per
1000,000 per birth has a prevalence of Proteus syndrome. This condition is also misdiagnosed [4].
Males are more affected rather than females [5].

3. PATHOPHYSIOLOGY

Proteus syndrome is not caused by anything before or during pregnancy and not caused by any
environmental exposures. [6]. NIH has recently recognized that gene called AKT1 mutation causes
Proteus syndrome. It is a mosaic alteration that produce a protein which acts like a switch that
controls the cell growth and interacts with other proteins controlling during its life cycle [7].
Alteration in AKT1 is called "c. 49G>A, p.Glu17Lys," an "activating mutation". Prevention of cell
death occurs as a result of protein produced by the mutation. NIH Studies by revealed that the
mutation occurs in particular cells and it is restricted to the effected cells and the cells proliferating
from the effected cells. Effected skin biopsy revealed that 75% mutation in samples. While only
30% mutation in unaffected tissue samples [8]. According to Lindhurst et al AKT1 mutations were
found in the affected tissues not in normal tissues. Proteus syndrome is a result of somatic
mutation, only cells which generate from the affected cell exhibit symptoms. Mutations in the
developing phase have a less severe phenotype. The random nature of the somatic mutation
explains in two components of phosphatidylinositol 3 kinase signaling pathway, which makes
Proteus syndrome a part of PTEN hamartoma tumor syndrome and AKT1 [9].
4. SYMPTOMS

Symptoms vary greatly from person to person which includes asymmetric overgrowth, raised, rough skin lesions may be with bumpy appearance, curved spine called scoliosis, fatty overgrowths often occur on the stomach, arms and legs. Non-cancerous tumors, often on the ovaries and membranes. Malformation of central nervous systems, causes mental disabilities and features such as a long face, narrow head, droopy eyelids, wide nostrils and also thickened skin pads on the soles of the feet [10]. Overgrowth usually begins between 6 to 10 months. Some patients can have brain overgrowth apparent at birth [11,13]. Overgrowth of lipomas locally or invasive lipomas and intrathoracic lesions that can be medically dangerous. Abnormal growth of
blood or lymphatic vessels can create vascular lesions [13]. Spleen and thymus are the internal organs affected and become enlarged during the disease progression. Individuals affected with PS have a susceptibility to develop tumors predominantly benign. Rare salivary gland tumors known as monomorphic adenomas may occur. Some individuals may develop cystic lung disease, kidney or urinary abnormalities and eye abnormalities such as crossed eyes, benign cysts or tumors of the eyeball. This disorder itself does not uniformly cause learning impairments, defective intelligence is also common among patients with proteus syndrome [14].

5. DIAGNOSIS

Molecular diagnosis is used to identify the causative gene alteration in AKT1. DNA diagnostic testing is performed on biopsies on affected tissues to know the presence of gene alteration in the blood. Other diagnostic techniques used are plain x-ray, computed tomography scans for skull lesions, high-resolution CT scan of the lungs for pulmonary cysts and brain, abdomen, limbs and pelvis MRI as well as ovarian masses were detected using Ultrasound [15].

5.1 General characteristics

Mosaic distribution indicates overgrowth only in some of the body parts which gives a patchy appearance. No one else in affected person’s family has features of overgrowth known as sporadic occurrence. Overgrowth alters the appearance of the affected body parts over time as Progressive course [16].

5.2 Specific characteristics
<table>
<thead>
<tr>
<th>CATEGORY A</th>
<th>CATEGORY B</th>
<th>CATEGORY C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Connective tissue nevus</td>
<td>1. Epidermal nevus</td>
<td>1. Dysregulated adipose tissues</td>
</tr>
<tr>
<td></td>
<td>2. Disproportionate overgrowth</td>
<td>2. Disproportionate overgrowth</td>
</tr>
<tr>
<td></td>
<td>Skull</td>
<td>Skull</td>
</tr>
<tr>
<td></td>
<td>Viscera</td>
<td>Viscera</td>
</tr>
<tr>
<td></td>
<td>3. Specific tumors before end of second decade</td>
<td>3. Specific tumors before end of second decade</td>
</tr>
<tr>
<td></td>
<td>Bilateral ovarian cystadenomas</td>
<td>Bilateral ovarian cystadenomas</td>
</tr>
</tbody>
</table>

---

Uncommon

1. Epidermal nevus
2. Disproportionate overgrowth
3. Specific tumors before end of second decade
4. Dysregulated adipose tissues
5. Vascular malformation
6. Facial phenotype
7. Venous and lymphatic malformation
5.3 Literature and Review

5.3.1 Viljoen (1987) manifestations of the Proteus syndrome in 6 patients. All had marked hypertrophy of the skin of the soles which was believed to be a unique feature of Proteus syndrome. Large epidermal nevi, linear macular lesions with areas of depigmentation and hyperpigmentation were seen in 3 patients. Light microscopic analysis demonstrated elongated basal cell cytoplasm [17].

5.3.2 Skovby (1993) reported 2 patients who illustrated 2 ways of spinal compromise development tumor infiltration. Spinal stenosis precipitated as a result of angular kyphoscoliosis in one of the patients. Cord compression occurred by the infiltration of a paraspinal, intrathoracic angiolipoma in the other patient.

Table 1 Specific characteristics of Proteus syndrome

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Paroid nomomorphic adenoma</th>
<th></th>
</tr>
</thead>
</table>

---
5.3.3 Cohen (1993) reported 2 unusual cases that supported the concept of somatic mosaicism. One patient was suffered from chest and abdomen covered with a huge connective tissue nevus as well as calvaria hyperostoses. He also reviewed selective aspects of Proteus syndrome, including uncommon neoplasms, abnormalities of lungs and kidney, malformations of brain and abnormality in craniofacial skeleton growth[18].

5.3.4 Smeet (1994) reviewed selective aspects of Proteus syndrome includes atypical neoplasms, abnormal kidneys and lungs, brain malformations, and types of abnormal growth in the craniofacial skeleton [19].

5.3.5 Battin (1996) described 2 unrelated children diagnosed at birth as having isolated macrodactyly. Examination showed the development of hemihypertrophy in both cases. 4 years old girl was observed with three dorsal angiomas. The symptoms of both of these patients better fit the diagnostic criteria of Proteus syndrome [20].

6. MANAGEMENT AND TREATMENT

In Proteus syndrome treatment physical and occupational therapy is very important. Designed orthotics such as special foot wares may require. Surgical removal of lesions are preferred if significant pain exists. Anticoagulation should be followed if deep vein thrombosis or pulmonary embolism. Regular examination is must to recognize the presence of tumors due to predisposition. Annual physical examination and radiography are also recommended [21]. Orthopedic procedures helps to delay or halt linear bone growth; rehabilitation medicine care including physical, occupational therapy such as correcting deformities of skeletal scoliosis, dermatologic care of skin abnormalities like cerebriform connective tissue nevi with pedorthist intervention is needed.
Bullous pulmonary disease should be monitored continuously. Psychosocial counseling for the benefit of the patient and family.

Studies on the benefits of Rapamycin in proteus syndrome was found to have a positive potential in the treatment. Phase 0 dose-finding trial of has been started by inhibitor ARQ 092 by the research team in the National Human Genome Research Institute at the US NIH. Tests on tissues and cell samples from patients proved the downstream targeting efficiency of AKT ARQ 092 and reduced phosphorylation of AKT [22,23]

**Figure.2 Treatment of Proteus syndrome**

![Treatment of Proteus syndrome diagram]

6.1 Generalized treatment

6.1.1 *Medical care*
Treatment for this disorder is through medicine called Rapamycin [24]. Immunosuppressant, Rapamycin systemic Rapamycin inhibits cytokine (Interleukin (IL)–2, IL-4, and IL-15) stimulated T lymphocyte proliferation and activation. This may inhibit antibody production. Binding of immunosuppressive complex with FK is the mechanism of the process. Protein-12 (FKBP-12). Although the sirolimus-(FKBP-12) complex is inactive against calcineurin activity, the complex binds to the receptor and inhibits activation of a key regulatory kinase is the target of Rapamycin (mTOR) in mammals. This is believed to suppress cytokine-driven T-cell proliferation, inhibiting cell cycle progression from G1 to S phase.

**Figure 3. Mechanism of action of Rapamycin**
Rapamycin is absorbed from GIT. 14% Bioavailability with approximately 92% protein binding. Attain $t_{\text{max}}$ in 1 to 3 hours, after oral administration. Peak blood concentration is $12.2 \pm 6.2$ and $37.4 \pm 21$ng/mL in renal transplant patients administered 2 mg and 5 mg respectively of Rapamycin cyclosporine and corticosteroid combination. The immunosuppressant effect of Rapamycin lasted up to 6 months after discontinuation of therapy. Major route of elimination is feces. Elimination half-life of sirolimus was found to be $62 \pm 16$ hours after multiple dosing in renal transplant patients. No information is available on the relationship of age to the effects of sirolimus. [25]. Rapamycin drug is a substrate for both cytochrome P-450 3A4 and p-glycoprotein. Inducers of these two may decrease Rapamycin concentration whereas inhibitors of both increase Rapamycin concentration. Rapamycin with cyclosporine combination increase drug concentration to avoid this Rapamycin has to be taken 4 hours after administration of cyclosporine [26]. Rapamycin tablets should be stored between 20°C to 25°C and oral solution should be stored between 2°C to 8°C and protect from light [27].

Rapamycin may cause a serious viral infection of the brain that can lead to disability or death. This risk is higher if you have a weak immune system or due to certain medicines. In case of any changes in mental state, problems with speech or walking, or decreased vision consult with doctor immediately because these symptoms may start gradually and get worse quickly. Increase the rate of mortality, graft rejection, and thrombosis in hepatic artery in liver transplant, lung transplant patients exhibit bronchial anastomotic dehiscence, hypersensitivity, dermatitis, Angioedema, Fluid accumulation along with wound healing impairment hypercholesteremia were also associated with rapamycin administration [28].

Drawback to long-term use of Rapamycin is increased insulin resistance. The research found that both dietary restriction and Rapamycin inhibited lipid synthesis, but only dietary restriction
increased the oxidation of those lipids in order to produce energy. The drug metformin can effectively overcome the concern since it has been used in diabetic patients to encourage oxidation of lipid. The studies were performed in humans on the effectiveness of the Metformin and Rapamycin in the treatment of aging and age-associated diseases were supported by the National Institutes of Health [29]. Case study revealed that a confirmed with Proteus syndrome at age of 16 months. At the age of 2 he was given oral Rapamycin at a low dose and it was well tolerated and caused no side effects. Within 2 months of treatment there was an increase serum albumin level and for 5 years he was able to walk independently. At 17 months of this therapy the drug was ceased to check the reversible antitumor effect. 12 weeks of cessation leads to respiratory difficulties but the biochemical evidence shows the resistance to growth of hormone was not affected by Rapamycin [30].

6.1.2 Surgical care

Prophylactic anticoagulation prior to elective surgery has suggested by clinicians. Surgical reduction or even amputation may preferred in extreme circumstances. For cosmetically important regions plastic surgery is preferred. Subcutaneous lesions should be considered and treated immediately once it start to obstruct vision or impinging vital structures. The size of the lipomatous lesion can be reduced employing laser lipolysis. This gives an advantage over surgical liposuction. Surgical resection may be helpful to prevent cystic lung malformations. The risk of the surgery includes the blood clot in the veins, bleeding, adverse reaction to anesthesia and overall risk of death [31].

6.1.3 Consultation
An orthopedist poses an important role in addressing the functional significance of both hemihyperplasia and scoliosis. A craniofacial surgeon or surgical team can address cranial asymmetry or hemifacial macrosomia. Cutaneous or subcutaneous lesions and its resectioning can be addressed by a plastic surgeon. CNS lesions such as cortical overgrowth, with or without hydrocephalus also in craniofacial procedures and operations can be done in the presence of a neurosurgeon with more accuracy. Successful evaluation of subcutaneous lesions and requirement of necessity of biopsies can be recognized by a dermatologist. Ocular involvement of the disease can be identified by an ophthalmologist. Dental anomalies can be treated by a dentist and orthodontist can handle malocclusion. A geneticist and genetic counselor can provide the patient and family with additional information about the diagnosis, diagnostic testing, proposed genetic mechanisms, and recurrence risks. A pediatrician can help with evaluating the learning disabilities of a child or developmental delays in a child, can include recommendations for therapy as well as schooling [32].

6.2 Personalize treatment

Epiphysiodesis may be especially useful to prevent or treat the skeletal overgrowth of proteus syndrome. Prophylaxis measures to prevent blood loss during surgery is necessary. The mainstays of treatment for Proteus syndrome include early identification of serious medical problems and the use of prophylactic and symptomatic treatment. Medical approaches such as Hemihyperplasia is limited to functional improvement. Macrodactyly makes difficulty normal functions [33]. Dental occlusion and mastication difficulties can be treated according to the patient. Hemifacial macrosomia or macroglossia is effective when cosmetic concerns are affected. Maxillofacial surgeon or craniofacial team consultation and care is necessary for PS patient. Lipomas can produce vascular malformations that create periodic evaluations compulsory throughout the
disease state. Laser treatment is effective in the removal cutaneous vascular markings and malformations. Permanent removal melanin-related hyperpigmentation is not possible with laser therapy. Approaches comprising CO₂ or ruby lasers, dermatome excision followed by phenol peel, cryotherapy, etc are found to be effective in individual patients in various degrees. Management of thrombosis is an important consideration due to its life threatening effects in patients with a palpable cord and respiratory distress. The risk of thrombosis is a major concern before surgery. MRI is a method to identify the chest and abdomen lesions such as pulmonary cysts lipomas [34].

7. RELATED DISORDERS OF PROTEUS SYNDROME

Hemihyperplasia a multiple lipomatosis syndrome characterized by the formation of multiple tumors of fatty tissues and the abnormal enlargement of one side or structure of the body the end resulting in unequal growth. Emihyperplasiamay indicates asymmetry between just one limb and another or between one half of the body and the other. Hemihyperplasia may be mildly progressive Encephalocranio cutaneous lipomatosis is an extremely rare disorder characterized by eye and skin abnormalities including tumors consisting of fatty tissues affecting the scalp and central nervous system and skin lesions consisting of improperly developed connective tissue. Some individuals have normal intelligence while others may experience intellectual disability. Seizures and porencephalic cysts have also reported. Klippel-Trenaunay syndrome is characterized by the presence of a capillary port wine stain on the skin with hypertrophy of the soft tissue and bone of that leg or arm and varicose veins. Maffucci syndrome that is characterized by benign cartilage overgrowths, skeletal deformities, and patches of skin as a result of cutaneous benign growths of blood vessel masses. Maffucci syndrome is inherited as an autosomal dominant trait [35].

8. CASE REPORTS
1. A case report in China was reviewed by Xi Bao Cai, Chang-Xing and Yan-Xia Cai. They present a 16-year-old girl with facial dysmorphism and verrucous hyperplasia on the right side of her body, who was deaf and exhibited more abnormalities as she grew. The physical examination showed that she had a normal intelligence but several anomalies. CT scan of her head and face showed large lipomas. ECG and ultrasound for organs was normal.

2. Keerthi Talari, Praveenkumar, Arinaganhali, Subramanyam Dharanitragada Krishna presents a case of a 50-year-old man with angina pain. They noticed the enlargement of his index and middle fingers of both hands and found that he had it from the age of 5. On examination, they found hypertrophy of involved fingers with a limitation of movements. His systemic examination was otherwise normal.

3. Article by MD Popescu, G.Burnei presents a case of a 5-year-old white male boy, who had a disproportionate asymmetrical overgrowth of lower limbs, feet, right calf and thigh. His facial phenotype was normal. In anterior part of calf two hard masses were identified by ultrasound. Under General Anesthesia an excision of important fatty overgrowth and lymphangioma of the posterior part of the right calf was performed [36].

4. This report was written by Minglin, Zhaojun Sun and Yong Dai. It is about a 34-year-old man in Europe who was admitted to Shenzhen hospital for the treatment of postnatal overgrowth and skin problems in limbs and hips. Affected tissue sample was collected from patients back for molecular biological analysis by whole-exome sequencing and found he had Proteus syndrome with multiple hemangiomas like lesions and systemic vascular disease. The patient refused surgery and treatment to control the skin and gastrointestinal symptoms. Treatment included mupirocin for infection of skin lesions. Condition remained stable and the symptoms were partially controlled.
5. A case report review by Satter E presents a 19 years old man from Nias Island of Indonesia. The patient had an enlargement of the left foot and vascular lesions on his left calf from the time of his birth but didn’t notice the foot size until he grew. Due to the vascular malformation there was an increase in his foot growth at age 7. Foot became thick and resulted in pain and difficulties in walking. A plain lateral radiograph of foot confirmed the enlargement of bones. [37].

9. CONCLUSION

Difficulty in the identification of AKT1 mutation at the early stages of the disease due to the absence of sensitive diagnostic techniques as well as the patient to patient variability in the signs and symptoms restrict the early diagnosis of proteus syndrome. This risk is especially great when the condition is polymorphous and variable in its expression and possibly falls under different medical disciplines. About 200 cases of proteus syndrome have been reported in the literature, yet the incidence of symptoms like ocular malformations has not known. Under such circumstances, important single observations need to be reported and studied. Patient centric therapy, care and new drugs are required for the effective treatment Proteus syndrome.

REFERENCES


