**Proteus Syndrome: A Review**

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**1. Introduction**

PROTEUS SYNDROME (PS) is also known as Elephant Man Disease/Partial Gigantism or Macrocephaly Syndrome. Proteus syndrome is named after the Greek sea-God Proteus, who could change his shape according to his will assuming many forms to escape capture. This name was given to represent the various clinical manifestations and morphological changes seen in the first patient identified with this syndrome. It is a hamartomatous syndrome, with clinical manifestations that vary greatly and predominance of malformations and overgrowth of multiple organs. It is an extremely rare syndrome with an estimated prevalence of approximately 1:10, 00,000 being more common among males at a ratio of 1:9:1**[1].**

**(**PS) is extremely rare but chronic or long term condition**. (**PS) is a complex disease characterized by malformations and overgrowth of different tissues mainly connective tissue, although any tissue may be affected in this disease **[2-4].**Bones, skin, blood vessels and central nervous system may also be affected due to this disease [**5-8].** The limbs, spine and skull are most commonly affected. Affected individuals may be complicated by premature death, mostly due to pulmonary embolism and respiratory failure. The disproportionate overgrowth of tissue is usually asymmetrical and involves the arms, legs, hands, feet’s, and digits. These overgrowths aren’t apparent at birth, but become more noticeable by age of 6 to 18 months. These overgrowths usually aren’t cancerous. The overgrowth can be mild or severe depending upon the type of body part affected. If these overgrowths are left untreated the overgrowths can lead to serious health and mobility issues **[4].**This disease is also characterized by a mosaic distribution, sporadic occurrence, and progressive course, hyperplasia of connective tissue, vascular malformations, epidermal nevus, and hyperostosis**.[1]** Clinical features may be present at birth but typically develop over time, starting between 6 to 18 months of age.**[9-18]** The postnatal, progressive, and asymmetrical overgrowth occurs in a mosaic pattern**.** Bone, connective tissue, fat, central nervous system, eye, spleen, thymus, and colon are commonly involved tissues [**1].**

**1.1 History of Proteus Syndrome (Ps)**

The syndrome is named after the Greek sea –god PROTEUS, who could change his shape. The condition appears to have been first described in the American medical literature by Samia Temtamy and John Rogers in 1976. American pathologist Michael Cohen discovered PS in 1979.In the year 1983, a German pediatrician Hans Rudolf Wiedemaan named the disease as PS, also called Ella Proteus or Elephant Man Disease. In 1979, Michael Cohen explained the disease to the community. The disease was first identified in a patient named Joseph Merrick whose head was about 36 inches, one of his fingers was 5 inches and the skin was covered with rough hard growths and smelled unpleasantly. These deformities developed during early childhood, being noted initially at about 18 months of age and progressed throughout the lifetime. When he was 20 a large portion of his facial deformity was successfully removed. When he was 22 his case was studied by Treves and brought to the meeting of the pathological society in London for further studies. However Merrick declined examinations and presentations. His figurative distortion until the end stage did not help in the diagnosis of the disease. Merrick died in the year 1890 at the age of 27 due to suffocation caused by the weight of his head as he lied down[**6].**In another case of a boy named Jordan 16 year old , Proteus syndrome (PS) started affecting the fingers, spine ,neck, and legs which became severe during the age of 14. Above the knee amputation and the use of prosthetic legs has helped him in walking. Overgrowth of limbs, skin lesions, and thickening of the soles of his feet was precipitated by the disease **[3]**.

**2. Epidemiology:** PS is very rare with <120 individuals confirmed affected with PS. 1 case/10.00, 000 births has a prevalence of PS. Males are more affected than females **[3].**

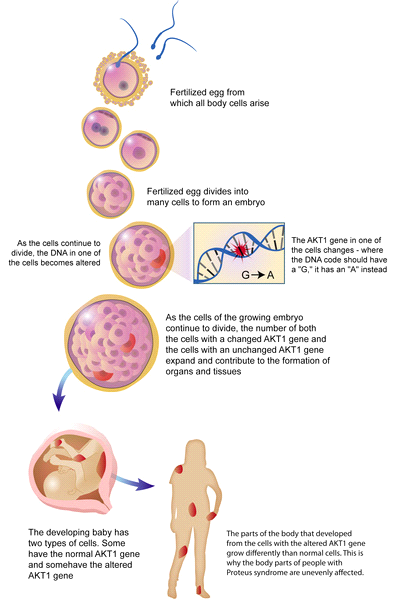
**3. Symptoms of Proteus Syndrome**

Symptoms of Proteus syndrome vary greatly from one person to another and can include the following **[3]**

* Asymmetric overgrowths, such as one side of the body have longer limbs than other.
* Rough, raised skin lesions that may have a bumpy, grooved appearance
* A curved spine also called as scoliosis.
* Fatty overgrowths on stomach, arms and legs.
* Non-cancerous tumors often found on the ovaries and membranes that cover the brain and spinal cord.
* Malformations of the central nervous system (CNS) which can cause mental disabilities and features such as long face and narrow head.
* Thickened skin pads on the soles of the feet **[4].**
* Cerebriform connective tissue nevi, epidermal nevi **[23,24].**
* Malformed blood vessels (vascular malformations) which increase the risk of life threatening blood clots **[25].**

**4. Causes of Proteus Syndrome**

Proteus syndrome (PS) occurs during fetal development. It is caused due to mutations or permanent alteration of the gene AKT1.The AKT1 gene helps to regulate growth. The cause of mutation is not known, but this mutation in the gene AKT1 is random and is not inherited. For this reason, Proteus Syndrome is not a disease that is passed on from one generation to the next **[4].** Scientist has discovered that the gene mutation is mosaic. That means that this gene mutation affects some cells in the body but not others. This concept greatly explains why one body side of the affected individuals is severely affected and not the other and why the severities of the symptoms vary so greatly from one person to another **[4].** As PS is probably caused by a post-zygotic mutation, it results in mosaicism which possibly explains the variability of manifestations and the monozygotic twins discordant for the syndrome. **[20, 21].**



**Figure 1: Diagrammatic Representation of Mutations that occur in the DNA of a Developing Embryo leading To Proteus Syndrome**

**5. Pathophysiology**

**PS** is not anything that is caused before or during pregnancy and it is not caused by any environmental exposure. The National Institute of Health (NIH) has recently recognized that mutation in the gene called serine/ threonine kinase AKT1 causes PS. Alteration in AKT1 is a “somatic-activating mutation.” NIH studies revealed that the mutation occurs in particular cells and restricts itself to the affected cells and progeny. The overgrowth switches to malignancy in cells by signaling pathway of phosphatidylinositol 3 kinases. AKT1 gene binds to phosphatidylinositol 3, 4, 5-trisphosphate, a second messenger and translocate to the cell membrane, where it gets activated. Activation occurs through phosphorylation process . Phosphorylation at the threonine 308 occurs by phosphoinositide-dependent kinase 1 and Phosphorylation of serine 473 completes the activation process with the help of mTORC2 complex. Stimulated growth factors induce phosphatidylinositol 3, which in turn increases the level of phosphatidylinositol 4,5-bisphosphate which is available for AKT1 activation. This will up regulate cell growth, proliferation, and down-regulate apoptosis process. According to Lindhurst et al., AKT1 mutation is found only in the affected tissues, not in normal ones. PS is a result of somatic mutation, which means only those cells which generate from the affected cells exhibit symptoms of PS. Mutations in the developing phase have a less severe phenotype. The random nature of the somatic mutation exhibits in two components of phosphatidylinositol 3 kinases signaling pathway, which makes PS a part of hamartoma tumor syndrome **[3].**

|  |  |  |
| --- | --- | --- |
| Inactive in quiescent cells due to low phosphatidyl inositol level   |  | | --- | | AKT1 GENE |   PDGF Activation of phosphatidylkinase  Translocation to cell membrane by the binding of pleksterin homology to phosphatidylinositol 3,4,5 triphosphate  AKT phosphorylation at theorinine 308 by phosphoinositide dependent kinase.  AKT phosphorylation at serine 473 by mTORC2 complex.  Completely activated AKT1 gene   |  | | --- | | Up- regulation of cell growth proliferation and down- regulation of |   Normal protection of Abnormal growth of cells from apoptosis cells.  Where **PDGF** is Platelet derived growth factor |

**Figure 2: Pathophysiology of Proteus Syndrome**

**6. Somatic Mosaicism Hypothesis in Proteus Syndrome**

**Somatic mosaicism** refers to the occurrence of two genetically distinct populations of cells within an individual, which are derived from a post-zygotic mutation. In contrast to inherited mutations, somatic mosaic mutations may affect only a portion of the body and are not transmitted to progeny [**5].**The affected cells causing localized overgrowth may derive from any germ line layer or combinations thereof. Somatic mutations arising early in ontogenesis are estimated to be the cause of the plethora of findings in Proteus syndrome **[7].**

Somatic mosaicism, which is lethal in the non-mosaic state, is the present hypothesis for Proteus syndrome and although some of the findings in the syndrome are consistent with this hypothesis, but it has not been proven. The etiology is unknown to date. However, some information is available. Proteus syndrome is rare, and less than 100 bona fide cases have been recorded. The male: female sex ratio is 1.9:1 (n = 96). Some overgrowth and asymmetry are present at birth in 17.5% population (n = 97). However, such findings are much more dramatic during postnatal evolution of the disease. If the category is enlarged to include any signs present at birth (e.g., additional features such as vascular malformations and epidermal nevi), 43.3%of population is affected (n = 97).Bone overgrowth and soft tissue overgrowth tend to plateau after adolescence, although there are some exceptions like an occasional neoplasm has been noted at age 20, 30, or older. Important consequences in Proteus syndrome include premature death in 20% population, particularly from deep venous thrombosis, resulting in pulmonary embolism.

The following figure shows the mosaic distribution of lesions which depends upon:

1. The size of the cell mass.

2. Cell mass with proposed somatic cell mutates **[5].**

**7. Complications of Proteus Syndrome**

Proteus syndrome can cause numerous complications. Some can be life-threatening.

1. A child may develop large masses (tumors). The risk of tumor development appears to be higher in patients with PS than in the general population. Most tumors associated with PS are benign (e.g., monomorphic adenomas), but 19% are malignant **[22].**These can be disfiguring and lead to severe mobility issues. Tumors can compress organs and nerves, resulting in things like a collapsed lung and loss of sensation in a limb. Overgrowth of bone can also lead to loss of mobility **[4].**

2. The growths can also cause neurological complications that may affect mental development, and lead to loss of vision and seizures **[4].**

3. People with Proteus syndrome (PS) are more prone to Deep Vein Thrombosis because it can affect blood vessels. Deep vein thrombosis is a blood clot that occurs in the body’s deep veins, usually in the leg. The clot can break free and travel throughout the body[**4].**

4. Lipomas, Lipohypoplasia and Dermal hypoplasia [**26].**

5.If a clot becomes wedged in an artery of the lungs, it is called a pulmonary embolism, it can block blood flow to various parts of the body and lead to death. Pulmonary embolism is a leading cause of death in people with Proteus syndrome. Common symptoms of a pulmonary embolism are:

* shortness of breath
* chest pain
* a cough that can sometimes bring up blood-streaked mucus**.[4]**

**8. Diagnosis Tests in Proteus Syndrome (Ps)**

Physicians follow diagnostic criteria for the diagnosis of PS. The diagnostic criteria have 2 categories of attributes (General and Specific) [**19].**The general attribute delineate the non-specific features of PS patients. The general criteria comprise of the identification of the mosaic distribution (occurrence of overgrowth is restricted to the specific area of the body), sporadic occurrence and progressive course of the disease. The disease is confirmed when all three characteristics from general criteria, along with one manifestation from category A, two features from category B and three features from category C coexists. If a patient does not have all three of these criteria, the diagnosis of PS is rejected. Specific criteria for the diagnosis of PS are mentioned in Table given below [**3].**

**Table 1: Specific tests for diagnosis of PS**

|  |  |  |
| --- | --- | --- |
| Category A | Category B | Category C |
| Connective tissue nevus | 1.epidermal nevus | 1. dysregulated adipose tissue, eg:lipomas |
|  | 2. Disproportionate overgrowth of limbs and vertebrae | 2. vascular malformations  Eg:capillary malformation, venous and lymphatic malformation |
|  | 3. Specific tumors before the end of the second decade. | 3. Facial phenotype e.g.: long face, open mouth at rest, dolichocephaly, low nasal bridge. |
|  | 4. disproportionate overgrowth of skull |  |

**Differential diagnosis:** Differential diagnosis is the process of differentiating and confirming the presence of PS from similar disease conditions such as Maffucci syndrome, neurofibromatosis type1, Parkes-weber syndrome, and encephalocranio cutaneous lipomatosis.

**Antenatal diagnosis:** Prenatal testing is not performed in most of the PS cases as PS is not inherited.

**Diagnostic tests in PS:**

The diagnosis of Proteus syndrome can be difficult as the condition is rare and many doctors are unfamiliar with this disease. However various types of molecular tests are employed in the diagnosis of gene mutations in PS that include targeted analysis to identify the mutation. Analysis of the multiple tissues is undertaken for the diagnosis of (PS). The analysis through genomic testing is also undertaken that involves genome sequencing and exon sequencing. In vitae PS test is the example of identification of AKT1 gene mutations **[3]** The diagnosis can be undertaken by using the method of biopsy**.** In this method the biopsy of tissue or tumor is done and the sample is analyzed for the presence of a mutated AKT1 gene. Secondly if the mutated gene AKT1 is found through the biopsy test then screening tests such X rays, ultrasounds and CT scans may be used to look the internal masses [**4].** Other diagnostic techniques used are Computed tomography scans, plain X-ray**,** high-resolution computed tomography (CT) scan of the lungs, brain, abdomen, limbs, and pelvis, magnetic resonance imaging (MRI) for ovarian masses detection [**3].**

**Case studies on diagnosis:**

1. Skovby et al (1993) studies two patients with spinal compromise in PS. In one of the patients, spinal stenosis resulted from an angular kyphoscoliosis, while in the second one, it resulted from infiltration of a paraspinal, intrathoracic angiolipoma.

2. Lacombe and Battin (1996) described two unrelated children diagnosed at birth with isolated macrodactyly. Examination showed the development of hemihypertropy in both cases. The 4 year old girl was observed with three dorsal angiomas.The symptoms of both of these patients fit the diagnostic criteria of PS.

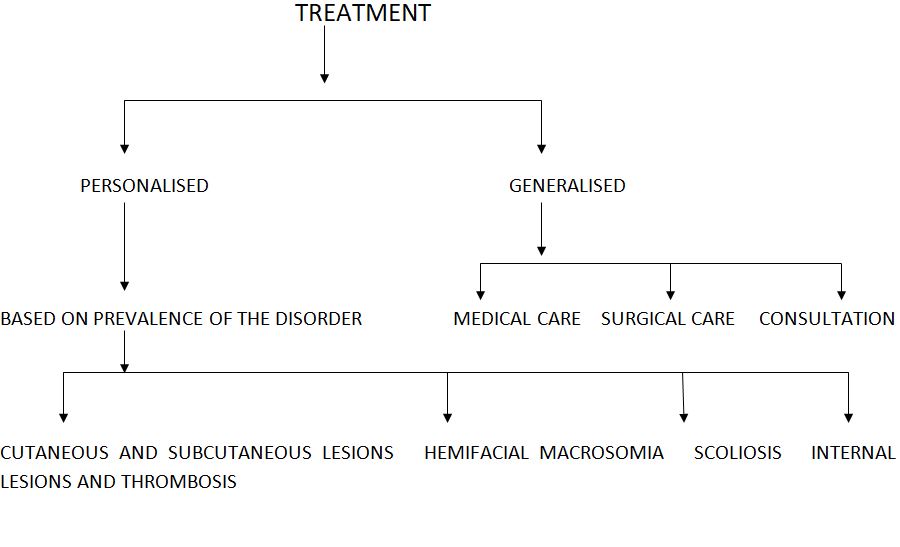
3.De Becker etal (2000) described a case on a 10 year old boy with PS who presented pericardial effusion and hypogammaglobulinemia, with IgG and IgA deficiency and low levels of antibodies to pneumococcal and hemophilus type B polysaccharides and lymphopenia. No cause was found for this immune deficiency leading the authors to suggest that it might represent an unrecognized feature of PS.

4. Slavotinec (2000) reported three patients with PS who died suddenly from a pulmonary embolism. The first patient who was diagnosed with PS at the age of 12 years who had varicose vein, portal vein thrombosis, right vein occlusion and recurrent pulmonary embolism. At the age of 25 he died from pulmonary embolism. The second patient was a 9 year old male who collapsed and died at home. An autopsy showed the cause of death was pulmonary embolism associated with deep vein thrombosis. The third case of a 17 year old female showed a large pulmonary embolus with no identified deep vein thrombosis in autopsy when the sudden death happened during sinusitis treatment.

5. Mohamed bhai et al (2002) Administration of misoprostol combined with prostaglandins was reported in mother with a baby having PS at 6 weeks gestation in an attempt to abort the pregnancy**.[3]**

**9. Management and Treatment of Proteus Syndrome**

Physical and occupational therapy possess a major role in the treatment of PS. Designed orthotics such as use of special footwear may assist the person with PS in walking. Rehabilitative medical care includes physical and occupational therapy such as correcting deformities of skeletal scoliosis. Orthopedic procedures help to delay or halt linear bone growth. An anticoagulant may also be used in case of deep vein thrombosis or pulmonary embolism. A periodic examination can recognize the pre-disposition of tumors. Annual physical examination may also be recommended in case of PS. Special care should be given to the dermatological abnormalities. If pain exists then surgical removal of lesions is preferred. The bolus pulmonary disease should be monitored continuously. Psychosocial counseling sessions are beneficial to the patients suffering from PS and also for the family. While considering the medicinal care, Rapamycin have found to have a positive potential in PS. Another drug is Mirasertib (ARQ 092inhibitor).The research has been performed by a team in the National Human Genome Research Institute at the USNIH. Different treatments available for PS are specified in the table [3].



**Figure 3: Treatment of Proteus Syndrome**

**Generalized Treatment**

**Medical care**: There is no approved drug for the treatment of PS. There are some existing treatments which are only for the symptomatic relief of the disease.

**Rapamycin**

Rapamycin is the only drug of choice for the treatment of PS which has been used as an effective immunosuppressant .The target of the drug Rapamycin is the gene AKT1. The mutation in this gene AKT1 provides an advantage of cell survival through phosphatidylinositol 3 kinase which is the target of the drug. Rapamycin.Sirolimus (FKBP) complex is inactive against calcineurin activity the complex binds to the receptor and inhibits activation of a key regulatory kinase phosphatidylinositol 3 kinase (mTOR) in mammals. Inhibition of the (mTOR) down-regulates the activation of 4E binding protein 1 as well as ribosomal protein S6.

**PHARMACOKINETICS OF THE DRUG RAPAMYCIN**: Rapamycin is well absorbed from the gastrointestinal (GI) tract. This drug has bioavailability of 14% with approximately 92%protein binding which is exhibited by this drug. Rapamycin plasma half-life of 1 to 3 hrs. after oral administration. Peak blood concentration of Rapamycin was observed to be 12.2and 37.4mg/ml in renal transplant patients when they administered 2 mg and 5 mg respectively of rapamycin in combination with cyclosporine and corticosteroid. The major route of elimination of rapamycin is through faeces.The elimination half-life of sirolimus was found to be 62 hrs after multiple dosing in renal transplant patients. There is no available information on the relationship of age to the effect of Sirolimus. Rapamycin drug is a substrate for both cytochrome P-450,3A4 and p-glycoprotein.Drug induction and inhibition can be produced by the substrates of these enzymes and their transporters. Rapamycin is administered 4hr after the administration of cyclosporine. Rapamycin tablets should be stored between 20°C and 25°C and oral solution should be stored between 2°C and 8°C and protected from light.

**ADVERSE EFFECT ASSOCIATED WITH THE DRUG RAPAMYCIN:**

1. The ADR associated with the drug Rapamycin is that it may cause a serious viral infection of the brain that can lead to disability or death. Drug interactions or immunosuppression can worsen this condition.

2. A person may experience changes in mental state, problems with speech or walking or decreased vision. In such cases a person has to consult the doctor immediately because these symptoms may start and worsen quickly after certain period of time.

3. Mortality, graft rejection and thrombosis in the hepatic artery are also reported in patients who administered rapamycin.

4. In liver transplanted and lung transplanted patients, drug can precipitate bronchial hy perceptivity, dermatitis, angioedema, fluid accumulation along with wound healing impairment.

5. Long term administration of Rapamycin can induce hypercholestermia in patients.

6. Long term administration of Rapamycin consumption can increase insulin resistance. The research revealed that both dietary restriction and Rapamycin inhibited lipid synthesis can cause insulin résistance. But the drug Metformin can effectively overcome this 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 ageing and age associated diseases with the support of NIH. The case study was on a patient diagnosed with PS at 6 months of age. His treatment started with oral rapamycin at a low dose when he was 2.The drug was found to be well tolerated and caused no side effects. Within 2 months of treatment it was found that there was an increase in serum albumin level and for 5 years he was able to walk independently. After 17 months of therapy the drug was ceased to check the reversible antitumor affect. The drug was ceased for 12 weeks and respiratory difficulties were observed, but the biochemical evidence showed the resistance to growth hormone was not affected by rapamycin.

**Miransertib (Arq 092)**

Even though drug therapy is not a part of standard PS care**.** Studies by Lindhurst etal suggested that ARQ 092is another drug for the disease ARQ092 is an orally active investigational drug which produces its action by inhibiting the isoforms of the gene AKT1 that is AKT1, 2, and 3 isoforms. This drug is currently under clinical trial phase. According to the information provided by the National Institutes of Health clinical center, the dose of ARQ 092 was determined in vitro using the cell obtained from the PS patient. The study demonstrated AKT1 phosphorylation with less toxicity. The study results hypothesize that the drug dose required for the treatment of PS would be lesser than the dose of drug required for cancer therapy since the aim of the therapy is to inhibit AKT signaling rather than killing the cells. The drug has also been studied for its effect on overgrowth in disease or vascular anomalies.

**Surgical care:** Surgical re-sectioning or even amputation is preferred in extreme cases. The clinicians suggest prophylactic anticoagulation prior to elective surgery. For cosmetically important regions plastic surgery is recommended. The subcutaneous lesions should be treated immediately once it starts to obstruct vision or implying vital structures of the body. The size of the lipomatous lesions can be reduced by employing laser lipolysis. Laser lipolysis has advantage over surgical liposuction. Surgical resection may be useful to prevent cystic lung malformations. The risk of the surgery includes the blood clot in veins, bleeding, adverse reaction to anesthesia and overall risk of death.

**Personalized treatment:** Personalized treatment involves understanding the pattern of mutation in AKT1 gene, the type of cells affected by the mutation and the stage at which the mutation occurs determine the severity and the symptoms associated with the disease. The uniqueness of manifestations among the patients necessitates the patient - centered therapy in PS. The early diagnosis of serious medical problems and the use of prophylactic and symptomatic treatment for functional improvement is the main stay of PS. Medical approaches such as Epiphysiodesis may be especially useful to the patient with skeletal overgrowth. A medical approach such as hemi hyperplasia is limited to functional improvement only. Macrodactyly impairs the normal functioning of hands and foot. Dental occlusion and mastication difficulties can be treated according to the patient concern. Hemifacial macrosomia is effective when cosmetic concerns of a patient are affected. Facial dysmorphism in a patient can be addressed by a maxillofacial surgeon or a craniofacial team. Patients with lipomas and vascular malformations postulate periodic evaluations throughout their life. Laser therapy is effective in the removal of cutaneous vascular markings and malformations. Permanent removal of melanin-related hyperpigmentation is not possible with laser therapy. Management of thrombosis is an important consideration due its life threatening effects in patients with respiratory distress. The risk of thrombosis is a major concern before surgery [**3].**

There’s no cure for Proteus syndrome. Treatment generally focuses on minimizing and managing symptoms. Surgery to remove skin overgrowths and excess tissue growths may be recommended by the doctors. Doctors may also suggest surgically removing growth plates in the bone to prevent excessive growth.

The (PS) condition affects many parts of the body, so patient may need treatment from several doctors, including the following:

* cardiologist
* dermatologist
* pulmonologist (lung specialist)
* orthopedist (bone doctor)
* physical therapist
* Psychiatrist [**4].**

**10. Disorders Related to PS:** There are several disorders that are related to Proteus syndrome.

1. Hemi hyperplasia is a multiple lipomatosis syndrome characterized by multiple tumors of fatty tissues and the abnormal enlargement of either sides of the body that is (asymmetrical growth).Hemi hyperplasia may indicate asymmetry between one limb and the another or between one half of the body and another.
2. Encephalocranio cutaneous lipomatosis is another extremely rare disorder related to PS which is characterized by eye and skin abnormalities including tumors of fatty tissues. Lipomatosis affects the scalp and central nervous system. Encephalocranio cutaneous lipomatosis is manifested by development of abnormal connective tissue in the form of skin lesions.
3. Some individuals have normal intelligence while others may experience intellectual disability. Seizures have also been reported in several cases.
4. Klippel- Trenaunay syndrome is identified by the presence of a capillary port wine stain on the skin with hypertrophy of the soft tissue, bone of that leg and arm.
5. Maffucci syndrome a PS related syndrome is characterized by benign cartilage overgrowths, skeletal deformities and patches of skin as a result of cutaneous benign growths of blood vessels. Maffucci syndrome is inherited as an autosomal dominant trait.**[3,25]**

**11. Case Reports**

1. A case in china has been reviewed by Zhang etal. The case presents a 16 years old girl with facial dysmorphism and hyperplasia on the right side of her body. She was deaf and exhibited more abnormalities as she grew. Her physical examination claimed that she had a normal intelligence but several anomalies. CT scan of her head and face showed large lipomas.ECG and ultrasound for organs were normal.**[3]**
2. Keerthi Talari, Praveen Kumar, Arinaganhali, Subramanyam Dharanitragada krishana presents a case of 50 year old man with angina pain. They noticed the enlargement of his index and middle fingers of both the hands and found that he had it from the age of 5. Hypertrophy of the fingers limited the normal functioning. His systemic examination was otherwise normal.
3. Article by Popsecu etal presented a case of a boy who has suffered from a disproportionate asymmetrical overgrowth of lower limbs, feet, right calf and thighs. His facial phenotype was normal. In the anterior part of the calf two hard masses were identified by ultrasound. Under general anesthesia an excision of the fatty overgrowth and lymphangioma of the posterior part of the right calf were performed.
4. A report by Ou et al. was about a 34-year-old man in Europe. The patient was admitted to shenzhen hospital for the treatment of post nasal overgrowth and skin problems in the limbs and hips .The affected individuals tissue samples were collected from the patient for molecular biological analysis by whole exome sequencing. Results were positive for Proteus syndrome. The patient refused surgery and treatment was then given to control the skin and GI symptoms. Treatment included the use of drug mupirocin for infection of skin lesions. The treatment was able to partially control the symptoms of the disease and condition remained stable.
5. A case report was reviewed by Satter which presented a 19 year old man from Nias Island in Indonesia. The patient had an enlargement of the left foot and vascular lesions on his left calf from the time of his birth but did not notice the foot size until it became thick and resulted in pain and difficulties in walking. Due to vascular malformations, there was an increase in his foot growth at the age of 7.A plain lateral radiograph of the foot confirmed the enlargement of the bones.
6. Satter presents another case of a 10 year old boy with vascular lesions on his right chest. During the examination, the physician observed asymmetrical enlargement on his chest and the vascular malformation extended up to the upper abdomen and flank. In addition cervical scoliosis and multiple large lipomas on his back were also identified [**3].**

**Conclusion**

Proteus syndrome is a relatively recently described and complex disease with a variable phenotype, and its diagnosis is challenging. Although AKT1 mutations have been identified as a cause of Proteus syndrome, the precise pathogenesis and etiology of this syndrome require further investigation.

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