Proteus syndrome: a brief review

Giovanni Monteleone[1], Paola Sinibaldi[2], Maria Michela D'Aloia[3], Maurizio Alimandi[3]

[1] Department of Biomedicine and Prevention, University of Rome Tor Vergata.

[2] Department of Science and Technology Education. University of Rome Tor Vergata.

[3] Department of Clinical and Molecular Medicine, Sapienza University of Rome.

Correspondence:

Giovanni Monteleone, Via Montpellier n. 1- 00133- Rome – Italy - e-mail: giovanni.monteleone@uniroma2.it
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Abstract

The Proteus syndrome is a rare mosaic syndrome, characterized by regional or localized areas of excess growth compared to equivalent normal parts of the body. In this review, we summarize the etiopathogenetic mechanisms responsible for tissue overgrowth anomalies and the diagnostic criteria utilized for the correct formulation of its diagnosis.

Keywords: Proteus Syndrome, AKT1 mutation, PTEN, hamartomata

Riassunto

La sindrome di Proteo (Proteus) è una rara sindrome di mosaicismo caratterizzata da aree localizzate di eccessiva crescita rispetto ad aree controlaterali normali. In questa review riassumiamo i meccanismi eziopatogenetici responsabili delle anomalie di crescita tessutale e i criteri diagnostici utilizzati per la corretta formulazione della diagnosi.

Parole chiave: Sindrome di Proteo/Proteus, mutazione AKT1, PTEN, amartoma

Proteus Syndrome

Proteus syndrome is a highly variable sporadic disorder characterized by an asymmetric and disproportionate overgrowth of body parts, including skeletal and connective tissues that causes asymmetry of the skull, body, arms and legs, and is very frequently associated with plantar hyperplasia, haemangiomas, lipomas, varicosities and the presence of epidermal nevi.

This syndrome was originally described in two patients by Cohen and Hayden[1], as a disorder characterized by overgrowth of multiple tissues, connective tissue nevi, epidermal nevi and hyperostoses. In 1983 Wiedemann et al.[2] gave the first exhaustive clinical description of the Proteus syndrome in 4 unrelated boys generally affected by a combination of partial gigantism of the hands and/or feet, hemihypertrophy, nevi, macrocephaly or other skull anomalies and visceral affections, with the presence or the tendency to develop subcutaneous tumors.

The newly described syndrome was initially classified as a congenital hamartomatous disorder, "undoubtedly genetically determined" and perhaps transmitted as autosomal dominant. At that time, the authors reasoned that the basic defects were likely due to the focal overgrowth of the cellular elements in skin, bone and connective tissues. The name Proteus for this syndrome refers to the sea Greek Goddess "Πρωτεύς", son of Oceanus and Tethys, able to change shape at will to avoid capture (Fig.1 A, B, C).

To date, Proteus syndrome is classified as a mosaic "overgrowth syndrome", characterized by regional or localized areas of excess growth compared to an equivalent part of the body. The molecular culprit of the lesions is an activating *AKT1* mutation (c.49G>A, p.Glu17Lys) in post-zygous cells[3] (Fig. 1 D). This missense mutation is responsible for the unbalanced growth/apoptosis ratio in cells that become more resistant to pro-apoptotic stimuli and more sensitive to survival factors. The somatic *AKT1* c.49G>A mutation accounts for the clinical manifestations affecting many organs and apparatus whose severity might depend on extension and perhaps localization. The number of cells that carry the *AKT1* c.49G>A mutation can be variable,

and the extension and severity of the lesions may range from small areas of overgrowth typically in soft tissues, bone and skin, to different types of abnormal growth in the craniofacial skeleton including brain malformations sometimes accompanied by intellectual disabilities, pulmonary and renal abnormalities, the possibility of thrombosis in the deep veins and the appearance of uncommon neoplasms.

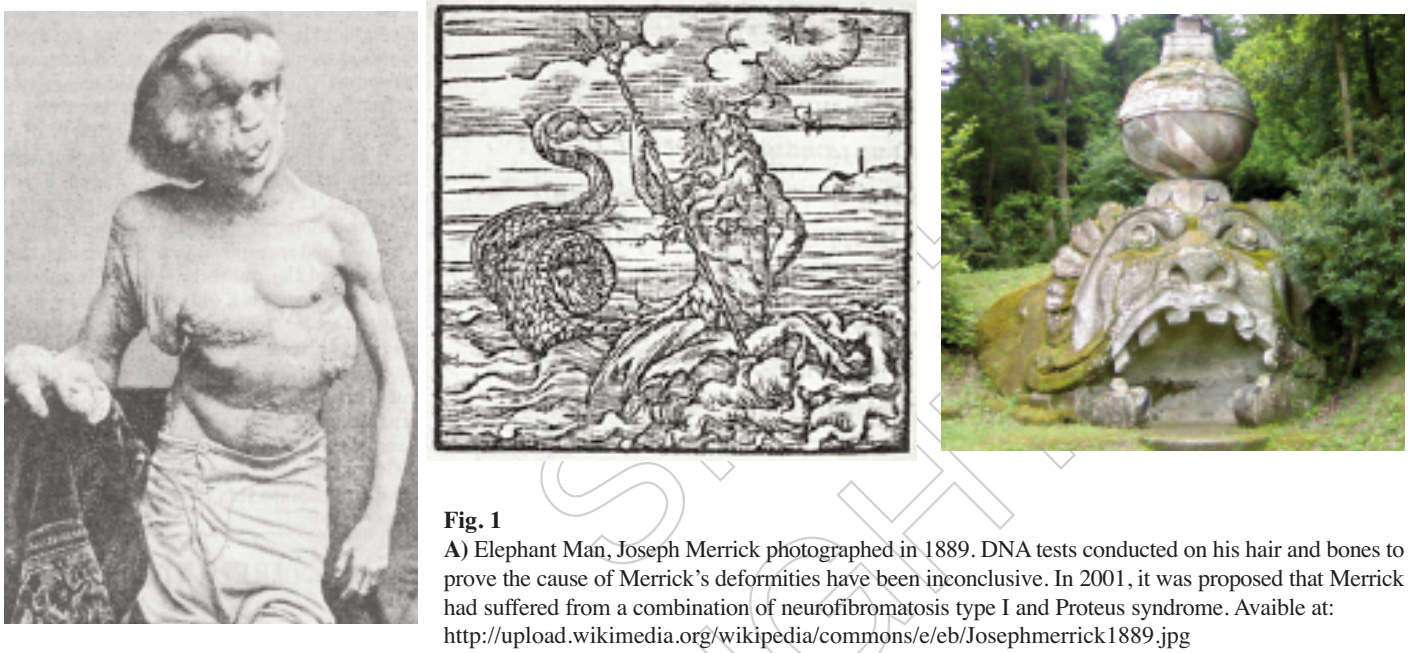

Fig. 1
A) Elephant Man, Joseph Merrick photographed in 1889. DNA tests conducted on his hair and bones to prove the cause of Merrick's deformities have been inconclusive. In 2001, it was proposed that Merrick had suffered from a combination of neurofibromatosis type I and Proteus syndrome. Avaible at: http://upload.wikimedia.org/wikipedia/commons/e/eb/Josephmerrick1889.jpg
B) Proteus envisioned by the Italian jurist and writer Andrea Alciato (1492-1550) Available at: http://upload.wikimedia.org/wikipedia/commons/1/1a/Proteus-Alciato.gif
C) The Proteus statue in "Sacred Grove" of Bomarzo (Rome, Italy second half of 1500)
D) The activating mutation c.49G>A in the PH domain of the AKT1 kinase generates a glutamic acid to lysine substitution at amino acid 17 (E17K).

The *AKT1* and the PI3K signaling pathway

Since its initial discovery as a proto-oncogene, the serine/threonine kinase *AKT1* (also known as protein kinase B or PKB) has become a major focus of attention because of its critical regulatory role in diverse cellular processes, including metabolism, proliferation, cell survival, growth, angiogenesis and tumor formation.

AKT1 is a downstream mediator of the phosphatidylinositol 3-kinase (PI3K) pathway. In general, the activation of PI3K occurs through the stimulation of the tyrosine kinases receptor. The recruitment of PI3K complexes at the receptor level occurs through the interaction between the phospho-tyrosine residues in the YxxM motives of the receptor (where Y is a tyrosine, M is methionine and x any aminoacid) and the SRC-homology 2 (SH2) domains of the PI3K p85 regulatory subunit. This interaction brings PI3K at the plasma membrane in close proximity to its substrate and relieves the inhibitory action of the p85 subunit over the catalytic subunit p110, which is then free to convert PtdIns(4,5)P_2 (PIP_2) into PtdIns(3,4,5)P_3 (PIP_3). PIP_3 serves as a second messenger that helps to activate *AKT1*, which is initiated by membrane translocation and occurs after cell stimulation and PIP_3 production.

In resting conditions, *AKT1* localizes at the plasma membrane bound with its pleckstrin-homology (PH) domain to the PIP_3, in association with the carboxyl-terminal modulator protein (CTMP). This ternary complex prevents *AKT1* from becoming phosphorylated. Two sequential regulatory mechanisms regulate the full activation of *AKT1*. The first event implies the phosphorylation of CTMP by a still unidentified kinase. Upon phosphorylation of CTMP, *AKT1* detaches from the complex and becomes a target for the kinase activity of PDK1 and PDK2 that phosphorylates the Thr308 and Ser473 residues, respectively (Fig. 2).

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Fig. 1

Fig. 2

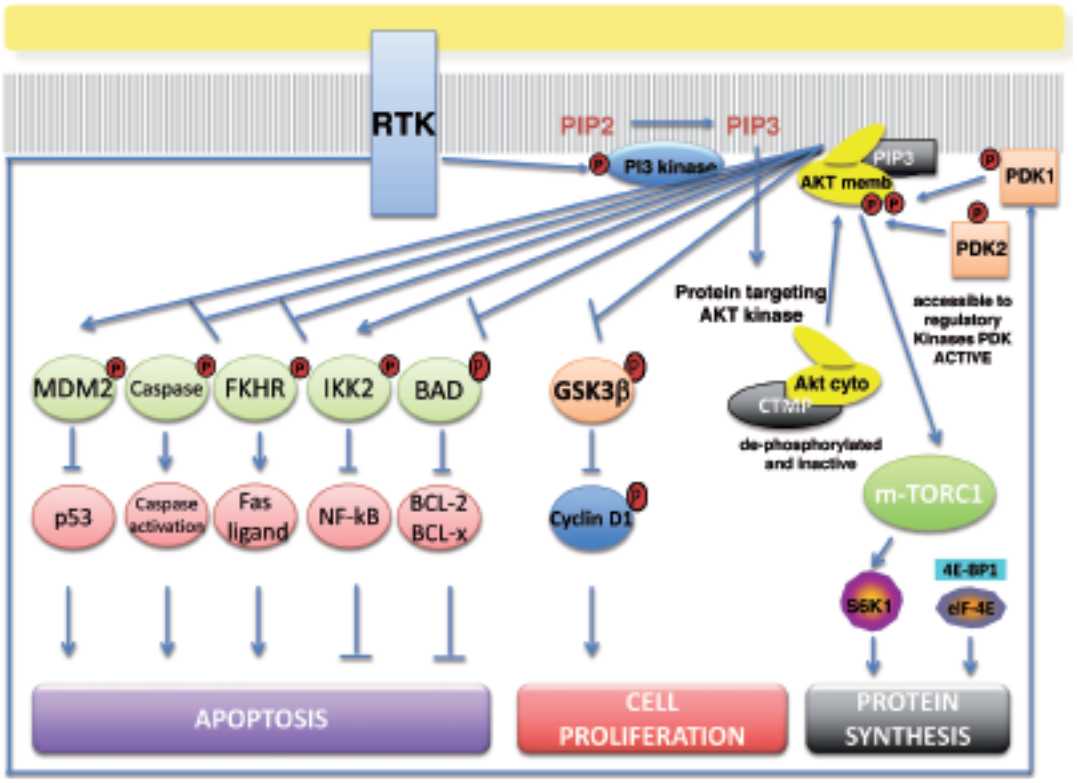

Fig. 2
The PI3/AKT pathway. Phosphorylation of AKT1 by PDK1 and PDK2 generates active forms of AKT. The AKT pathway negatively regulates the apoptotic programs while sustains survival and cell growth.

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Table 1: Functions of AKT

Inhibition of apoptotic programs	Sustaining of survival and cell division
AKT1	*AKT1*
Inactivates the proapeptic factors Bad and (pro)caspase-9	The overexpression mediates an increase in cellular response to growth factors
Activates IKK enhancing NFκB transcriptional activity on antiapoptotic genes	Promotes cytoplasmic localization of CKIs, such as p21 and p27, thereby inhibiting their function
Inactivates Forkhead transcription factors, inhibiting FasL synthesis	Stabilizes cyclin D1 e D3 levels
	Facilitates MDM2 nuclear localization and its inhibitory action on p53

Table 2. Diagnostic Criteria for Proteus Syndrome

DIAGNOSTIC FLOWCHART FOR THE PROTEUS SYNDROME	
CLINICAL CRITERIA	GENETIC CRITERIA
Specific Criteria	**Mosaicism**
General Criteria	AKT1 c.49G=>A, p.Glu17Lys

SPECIFIC CRITERIA	GENERAL CRITERIA
Mosaic distribution of lesions	Category A
Sporadic occurrence	Two from category B
Progressive course	Three from category C

	SPECIFIC CRITERIA CATEGORIES	
Category A	**Category B**	**Category C**
1. Cerebriform connective tissue nevus	**1.** Linear epidermal nevus	**1.** Dysregulated adipose tissue: either one
	2. Asymmetric disproportionate overgrowth of one or more:	a) Lipomas
	a) Limbs – Arms/legs – Hands/feet/digits Extremities	b) Lipohypoplasia
	b) Hyperostosis of the skull	**2.** Vascular malformations:
	c) Hyperostosis of the external auditory meatus	a) Capillary malformation
	d) Megaspondylodysplasia	b) Venous malformation
	e) Viscera: Spleen/thymus	c) Lymphatic malformation
	3. Specific tumors before 2nd decade: one of the following	**3.** Facial phenotype (only occurs with severe intellectual disability and/or seizures)
	a) Ovarian cystadenoma	a) Dolichocephaly
	b) Parotid monomorphic adenoma	b) Long face
		c) Downslanting palpebral fissures and/or minor ptosis
		d) Low nasal bridge
		e) Wide or antiverted nostrils
		f) Open mouth at rest

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Table 3.

Differential Diagnosis
Klippel-Trenaunay syndrome
Parkes Weber syndrome
Maffucci syndrome
Neurofibromatosis, type I
Epidermal nevus syndrome (formerly epidermal nevus syndrome or Solomon syndrome)
Bannayan-Riley-Ruvalcaba syndrome
Hemihyperplasia/lipomatosis syndrome
Familial lipomatosis
Symmetrical lipomatosis
Encephalocraniocutaneous lipomatosis

Table 4.

Guidelines for Patient Evaluation
Serial clinical photography
Initial skeletal survey with targeted follow up radiographs
MRI of all clinically affected areas: chest and abdomen in absence of symptoms
Dermatology consultation biopsy when indicated
Orthopedic consultation; operation when indicated
Ongoing genetic/pediatric management
Other consultations as indicated
Referral to family support group

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The downstream effects of the activation of *AKT1* converge to stimulate cell survival and proliferation, while promoting the loss of function of pro-apoptotic genes and the gain of function of anti-apoptotic molecules, through various mechanisms.

In cells, proliferation and survival are two distinct programs governed by two different pathways. The functions of *AKT1* are mainly directed to regulate this delicate balance by inhibiting cell cycle arrest through the phosphorylation of the cdk inhibitors p21 and p27 and, in the meantime, by promoting the expression of cell survival proteins stimulating the activity of NF-B. On the other hand, *AKT1* regulates the anti-apoptotic effects maintaining the suppressive activity of target genes that promote apoptosis, including Bad, forkhead and caspase 9.

Additional mechanisms have been described as a consequence of the activation of the PI3K/AKT signaling pathways, like the modulation of p53 functions and suppression of the PTEN phosphatase. By phosphorylating Mdm2, *AKT1* induces its translocation into the nucleus where it binds to p53, transfers ubiquitin molecules to p53 and targets it for degradation by the proteasome. On the other hand, the inhibition of the PI3K signaling pathway by PTEN, including *AKT1*, has the effect of maintaining Mdm2 in cytoplasm where it will be degraded. In this way, PTEN protects p53 from Mdm2 and allows cells to respond to damage or mutation with an apoptotic response.

Knowledge regarding *AKT* functions also arises from the findings that mutation in the coding sequence have been reported to occur in cancer, although at a very low frequency. The activating mutation c.49G>A in *AKT* that results in a glutamic acid to lysine substitution at amino acid 17 (E17K) in the lipid-binding pocket of the pleckstrin homology (PH) domain of *AKT* has been found in breast, colorectal and ovarian human cancers[4]. It is ha been suggested that the 17 Lys alters the electrostatic interactions of the pocket and forms new hydrogen bonds with a phosphoinositide ligand. This mutation occurring in the regulatory domain of *AKT* activates *AKT* by means of pathological association with the inner leaf of the lipidic bilayer and constitutive activation of the kinase domain. This results in a constitutive stimulation of downstream signals in cells that acquire advantage of growth and increased possibilities to be transformed.

Despite the complexity of the pathways that govern the *AKT* functions, its roles in the inhibition of the apoptotic programs and in sustaining survival and cell division have been clearly elucidated [5,6] and listed here in Tab. 1.

The diagnosis of Proteus syndrome

Proteus syndrome is a rare condition whose prevalence is difficult to estimate but affects 1:1,000,000 – 1:10,000,000 people on earth. Newborns have few or no signs of the condition, but the clinical manifestations of the overgrowth become apparent between the 6th and the18th month after birth with the tendency to become more severe over time.

The guidelines for the evaluation of these patients and the recommendation of the diagnostic criteria for the differential diagnosis were presented at a workshop held at the National Institute of Health in Bethesda (MD, USA) in 1998. They include a list of "General" and "Specific" Criteria that have been then reviewed by Biesecker et al.[7], lately by Turner[8] and Cohen[9] and are reported here in Tab. 2.

General Criteria

The General Criteria for the diagnosis and clinical evaluation of the Proteus syndrome include three major characteristics that need to be present: A) The mosaic distribution of the lesions; B) their progressive course; C) the sporadic occurrence of the disease. The concomitant presence of all these criteria is considered mandatory, regardless of the specific manifestations in a given patient.

Specific Criteria

The presence of Cerebriform connective tissue nevus is sufficient for the diagnosis and is almost pathognomonic for Proteus syndrome. Connective tissue nevi are common and are facultative but not obligatory, which means that they may or may not be present. They have been recorded most frequently on the plantar surface of the feet, but can also be on the abdomen, hands and nose[7,8].

The proposed criteria are so robust and highly predictive, that molecular genetic testing may be useful to confirm the diagnosis in patients where the clinical findings are ambiguous or mild. Nevertheless, few signs are pathognomonic, such as: A) the distorting and progressive overgrowth of the skeleton which is characteristic in Proteus syndrome and quite distinct from that of most overgrowth syndromes. The initial manifestation of the skeletal overgrowth characteristically around the 1st year and usually not later than the 12th year of age. B) The Cerebriform connective tissue nevi present in most individuals with Proteus syndrome, commonly found on the

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plantar foot, hand or ear. C) The linear verrucous epidermal nevus, appearing pigmented and rough, which can be present anywhere on the body. D) Adipose dysregulation, most commonly manifests as "lipomatous" overgrowth rather than lipoatrophy. E) The vascular malformations that include cutaneous capillary malformations and prominent venous patterning or varicosities.

Genetic Criteria

To date, the diagnosis of Proteus syndrome is facilitated by the molecular identification of the c.49G>A mutation in *AKT1*. This has been identified in most of the cases studied[3]. More than 90% of the patients who meet the clinical criteria for Proteus syndrome have a somatic mosaic mutation in *AKT1* and persons who do not meet these criteria do not have mutations in *AKT1*. The c.49G>A mutation is not inherited, but arises randomly in one cell during the early stages of development, usually before birth. As cells continue to grow and divide, some of them will have the mutation and other cells will not, up to until they generate a genetic mosaic.

However, mutational analysis conducted on a still small sample of patients, revealed that approximately 50% of Proteus-like syndromes and up to 20% of classic Proteus syndrome ascertained by the canonic diagnostic criteria[12] carry germline loss-of-function PTEN mutations[13]. This is not surprising since PTEN is a phosphatase that negatively controls PI3K activity and *AKT* functions.

Germline PTEN mutations have been identified in the Cowden syndrome (CS)[14] and have also been described in a subset of patients affected by the Bannayan-Riley-Ruvalcaba (BRR) syndrome, in 50% of the Proteus-like syndrome and in some Proteus syndromes[15,16].

Cowden syndrome is a disorder characterized by multiple hamartomata and an increased risk of developing several types of cancer, particularly cancers of the breast, thyroid and endometrium.

BRR syndrome is characterized by macrocephaly, hamartomata, lipomatosis, hemangiomatosis and dark freckles on the penis in males.

Proteus-like syndrome has the clinical features of Proteus syndrome but lacks some of the required criteria necessary for diagnosis. In fact, mutations in *AKT1* have not been reported in these patients. It is possible that Proteus-like patients will have somatic mosaic or germline mutations in genes encoding other components of the PI3K signaling pathway, including a number of genes that have been implicated in oncogenesis and/or overgrowth.

- *AKT2* mutations cause adipose dysregulation and hypoglycemia[17].
- *AKT3* mutations can be the cause of hemimegencephaly[18].
- *PTEN* mutations are known to cause both Cowden syndrome and segmental overgrowth phenotypes that overlap with, but are clinically distinct from, Proteus syndrome.
- *PIK3CA* mutations have been demonstrated in a number of clinically diverse overgrowth syndromes including CLOVE syndrome[19] and a phenotype termed "Fibroadipose overgrowth"[3].

Differential Diagnosis

The clinical diagnosis of the Proteus syndrome might be difficult in some cases, due to the presence of overlapping signs common to the BRR syndrome. Typical findings in the Proteus syndrome are hemihypertrophy, macrodactyly, exostoses, skin lesions, scoliosis and the sporadic occurrence typical of the mosaicism, meanwhile the patients with BRR syndrome have macrocephaly and related craniofacial findings. In particular, macrocephaly is reported be present in all the patients with BRR syndrome, while it is present only in 14% of patients affected by Proteus syndrome. The major overlapping sign includes the presence of hamartomata, which is the clinical expression of molecular lesions etiologically or pathogenetically related[20].

Areas of deficient growth which are characterized by partial lipohypoplasia and patchy dermal hypoplasia involving few areas of the body, can be present in many cases of Proteus syndrome. However, when these hypoplastic lesions are large and are accompanied by few and rather mild lesions of disproportionate overgrowth, the differential diagnosis needs to be done with the Elattoproteus syndrome, the inverse form of Proteus syndrome. In the Elattoproteus syndrome, the coexistence of hyperplastic and hypoplastic lesions might be explained by the occurrence of somatic recombination at an early stage of the embryogenesis that gives origin to two different cell populations, homozygous for either alleles and responsible for either excessive or defective tissue growth. The pathogenetic hypothesis indicated by Happle[21] sustains the coexistent expression of a Pleioproteus allele responsible for the overgrowth of tissues (from Greek πλείων, pleion: plus), with an Elattoproteus allele (from Greek ἔλαττον, elatton: minus) responsible for hypoplastic growth.

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CLOVES Syndrome (Congenital, Lipomatous, Overgrowth, Vascular Malformations, Epidermal Nevi and Spinal/Skeletal Anomalies and/or Scoliosis) is a very rare syndrome diagnosed in about one hundred and thirty people so far, identified simultaneously but independently by Saap et al. and Alomari[22,23]. All reported individuals with CLOVES and fibroadipose hyperplasia had somatic mosaicism for mutations in the *PIK3CA* gene. In Tab.3 and Tab.4, the list of syndromes to be considered for the differential diagnosis with the Proteus Syndrome are reported, together with guidelines for the correct clinical evaluation.

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