PROTEUS SYNDROME
Diagnosed in a male adult

Mohammed Mohy Eldin Selim *
Yaseen Al-Humaidan **
Hamda Al-Ansari

Abstract:

A case of Proteus Syndrome in an adult male diagnosed on clinical findings mainly cerebriform thickening of soles and palms, macrodactyly, inequality of growth of lower limbs, decreased subcutaneous tissue, arched palate, mental retardation, crumbled toes, deformed feet, widely separated nipples, webbed neck and hypogonadal features with smooth hypotrichotic skin.

Introduction:

Proteus Syndrome (PS) was first described by Wiedemann 1983[1]. The name is derived from the Greek god Proteus [old man of the sea who could change his shape at will to avoid capture].

PS has enormous morphologic variability and includes a variety of birth and developmental defects [2]. One of the major diagnostic criteria of PS is hypertrophic thickening involving plantar and or palmer surfaces with cerebriform appearance [2,3,4] which is considered by some authors to be pathognomonic of PS [4]. The thickening is due to increase in collagen in papillary and mid dermis [2]. Other major clinical findings diagnostic of PS are macrodactyly; hemihypertrophy; unilateral macrocephaly; dysmorphic growth; exostoses scoliosis; epidermal nevi, subcutaneous masses due to mesodermal hamartomas or lipoma, lymphangioma, hemangioma and fibroma [4,5,6,7,8]. The PS appears sporadically and some manifestations are already present at birth but the majority appears during early childhood [2].

Case Report:

A male 26 years old from Saudi Arabia was born after normal full term pregnancy and delivery. His family history was negative for consanguinity or similarly affected relative. On examination he showed

Thickening of both soles with classic cerebriform and gyriform appearance with warty painless masses at various parts of soles and heels and both feet were deformed with crumbled toes [Fig. 1, 2, 3, 4, 5, 6, 7, 8, 9]

Thickened palms with cerebriform appearance [Fig.10]

Asymmetric growth of both hands which are grossly disfigured with evidently thickened folded skin and thickened stubby fingers and a long thickened left fore finger [Fig.11].

Disproportionate and inequality of growth of lower limbs manifested by a taller right than left limb [Fig.12].

Inequality of growth of both upper limbs with disproportion between growth of upper and fore arms and thickening of skin of both fore arms [Fig.13,14].

Other features were: widely separated nipples [Fig.15]; relatively thin legs due to decreased subcutaneous tissue with scar like discoid patches [Fig.16]; hypogonadal features with relatively big eyes, small ears and generally smooth hypotrichotic skin [Fig.17 & 18], arched palate, webbed neck [Fig.19]. The diagnosis of Proteus syndrome (PS) was made on these clinical findings which are among the characteristic and diagnostic criteria of this syndrome.

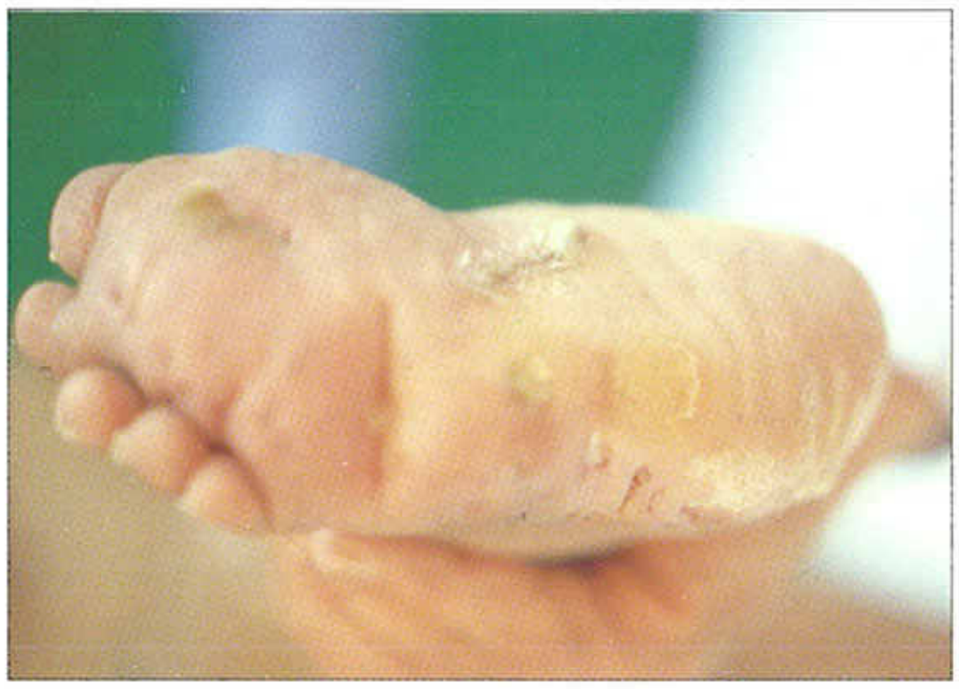
Discussion:

PS is a rare hamartomatous disorder characterized by multifocal overgrowth that can involve any structure of the body. PS is a rare disorder and leads to functional disability, cosmetic and psychosocial problems. PS is difficult to diagnose owing to its low incidence and to the late recognition of its identity.

The features of the syndrome may be present at birth but become more apparent with time [7]. Abdominopelvic cystic lymphangioma as part of Proteus syndrome was diagnosed prenatally [8]. Samlaska et al [3] reported 56 clinical findings in 34 published cases of PS and sub-classified them into two groups.

The first comprised about 18 major findings and the second listed 38 associated clinical findings. A major finding has been defined as the one identi-

* *Department of Dermatology & Venereology*
Hamad Medical Corporation
P.O. Box: 3050 - Doha ñ Qatar.
** *Chairman of Dermatology Department*
Dammam Central Hospital
Dammam Eastern Province
Kingdom of Saudi Arabia.



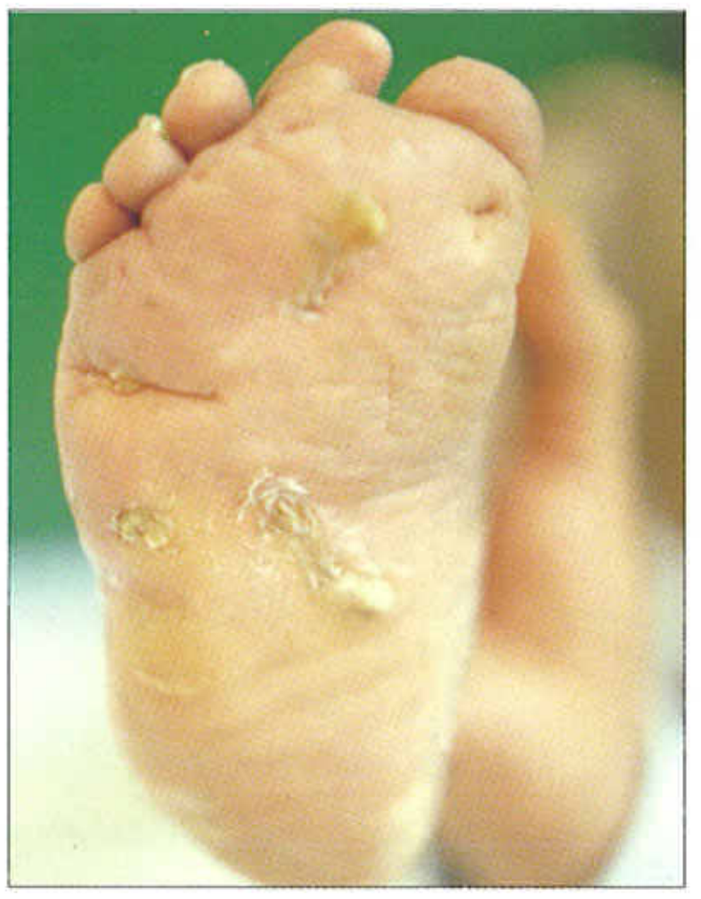
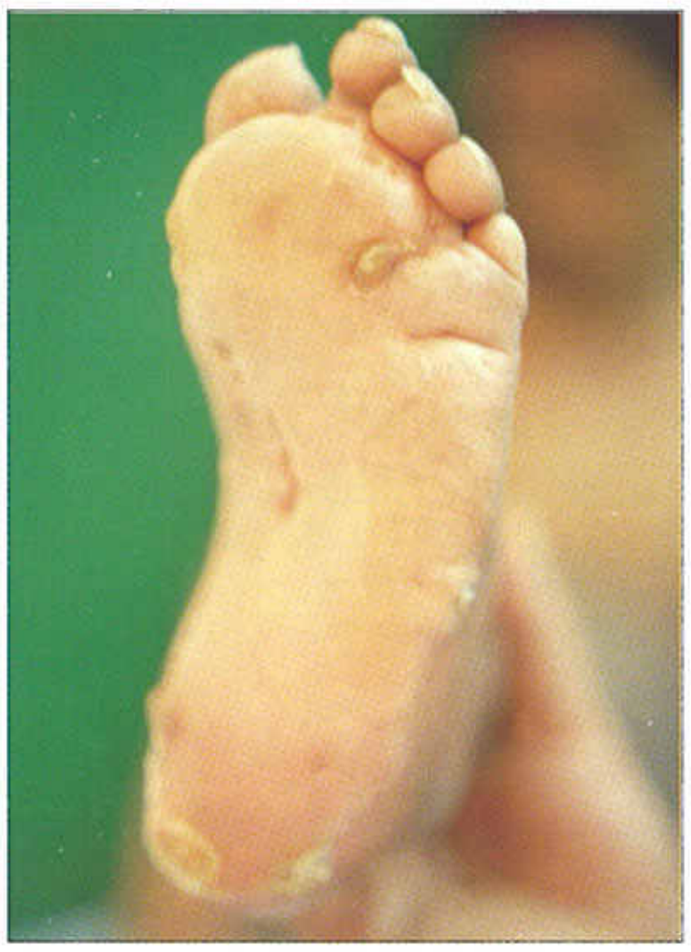


Fig. 1, 2 thickened sole of right foot with cerebriform and gyrate appearance



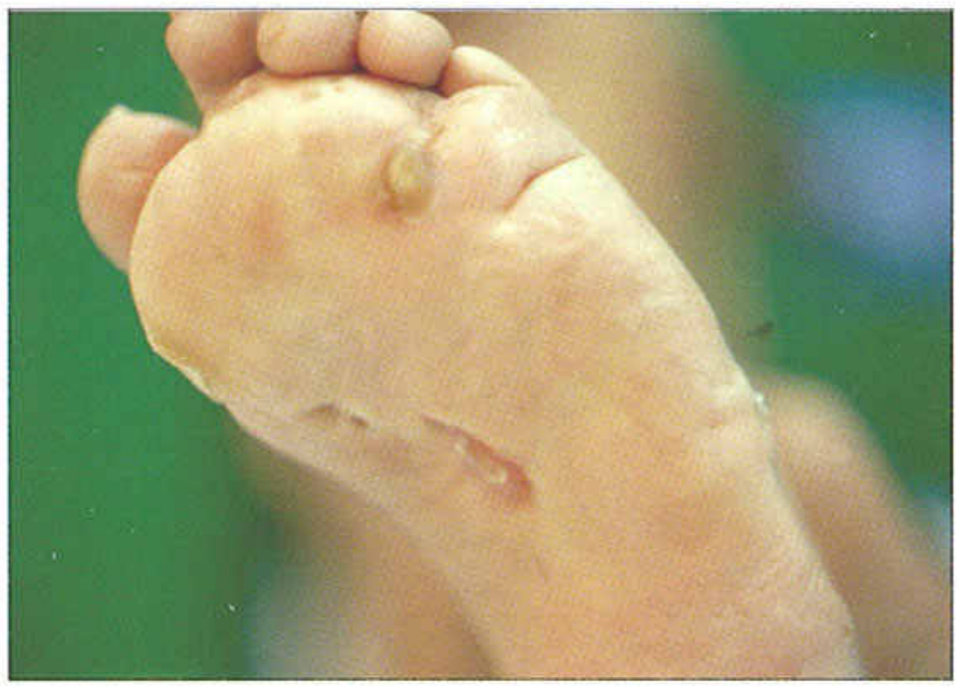
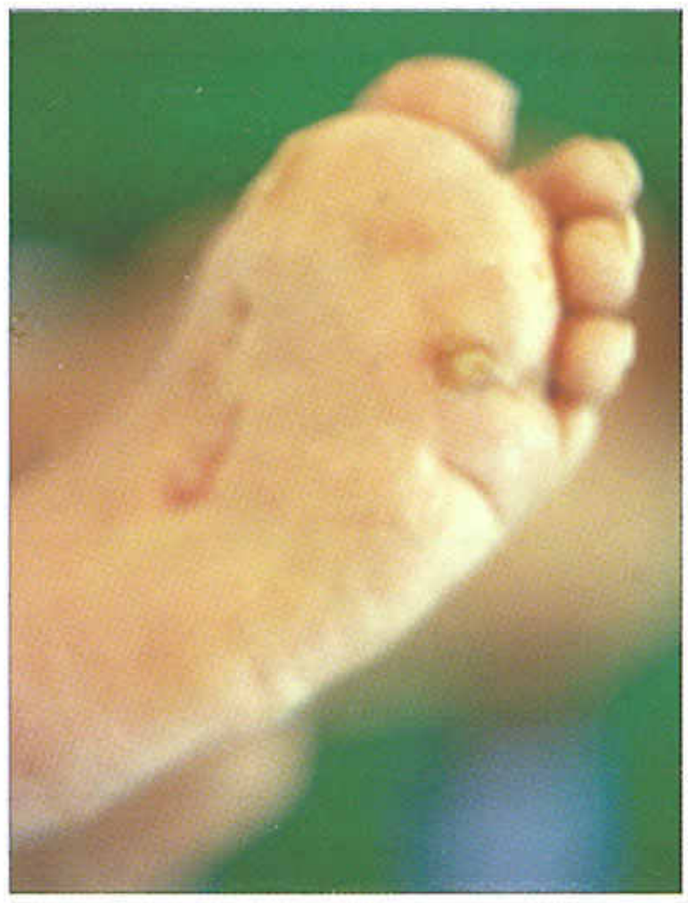
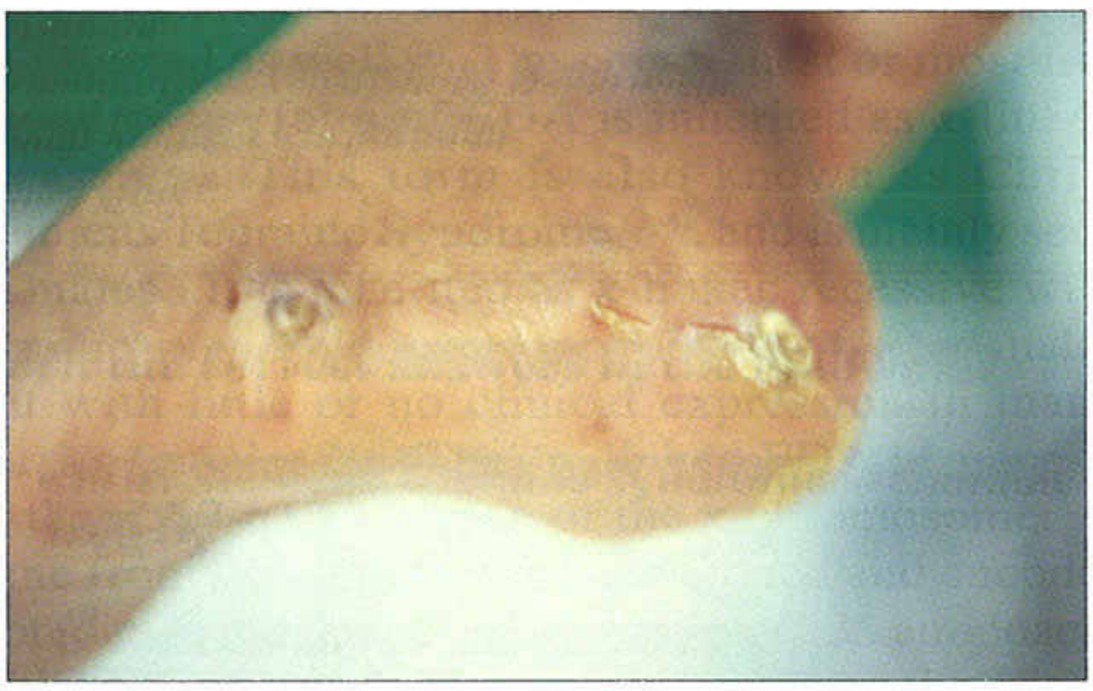


Fig. 3, 4, 5 thickened of left foot mainly at lateral side and sole of left foot with cerebriform and gyrate appearance and localized nodules.





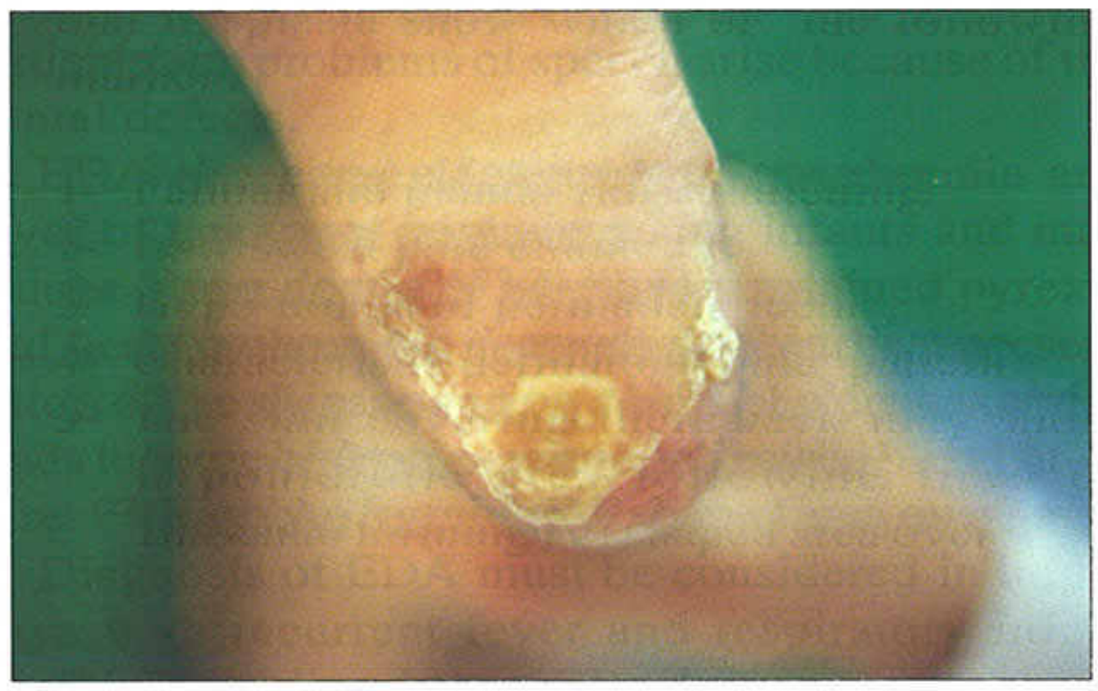
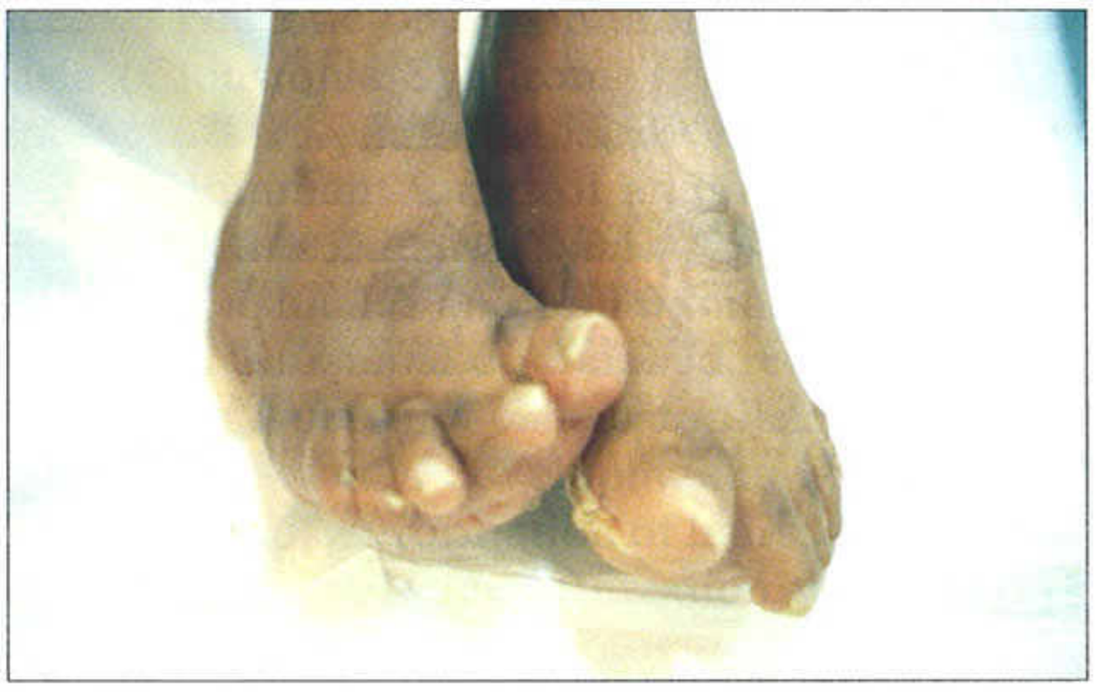


Fig. 6, 7 localized nodular thickening of sole heel.



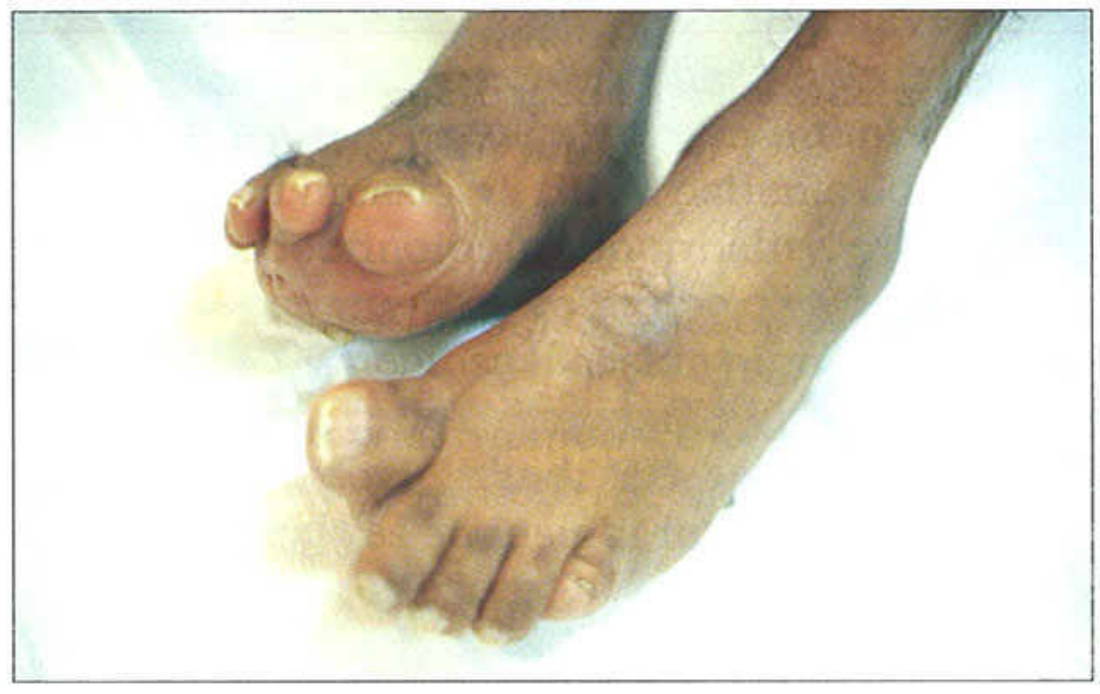


Fig. 8, 9 crumbled toes and deformed feet

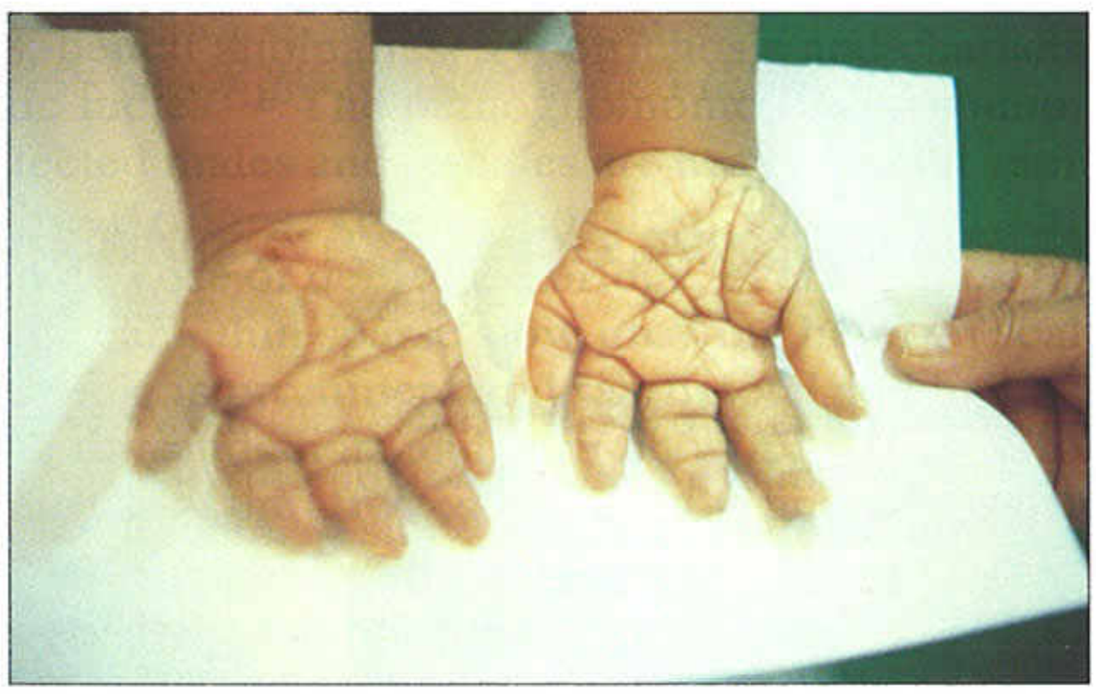


Fig. 10 cerebriform appearance of both palms

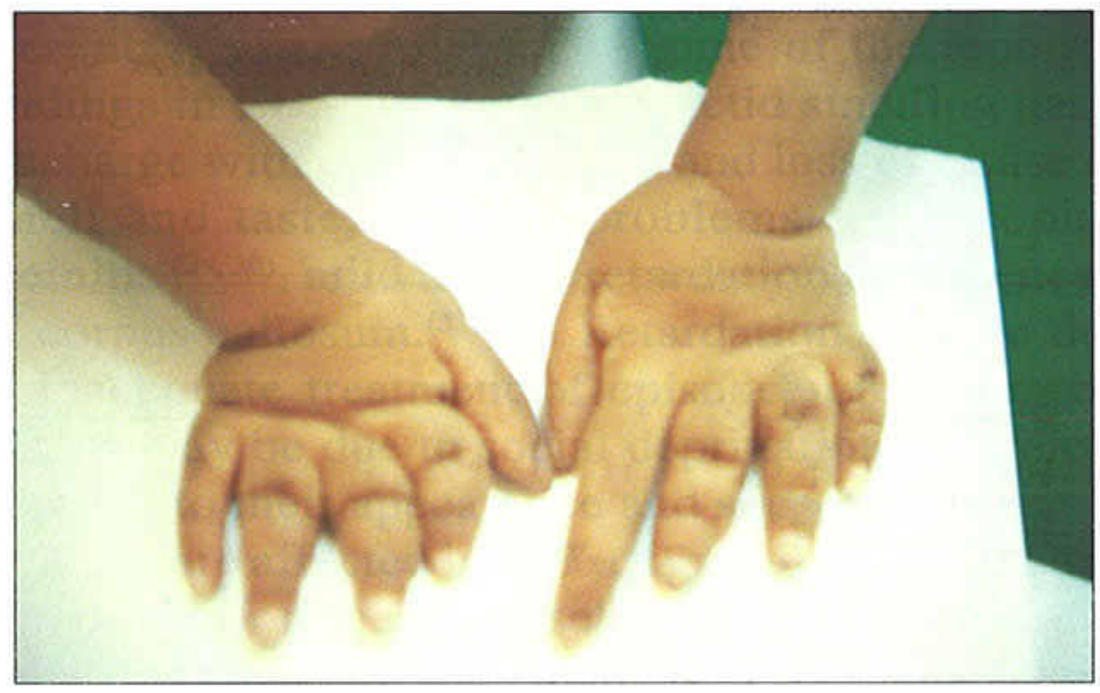


Fig. 11 shuby fingers with macrodactly of left forefinger

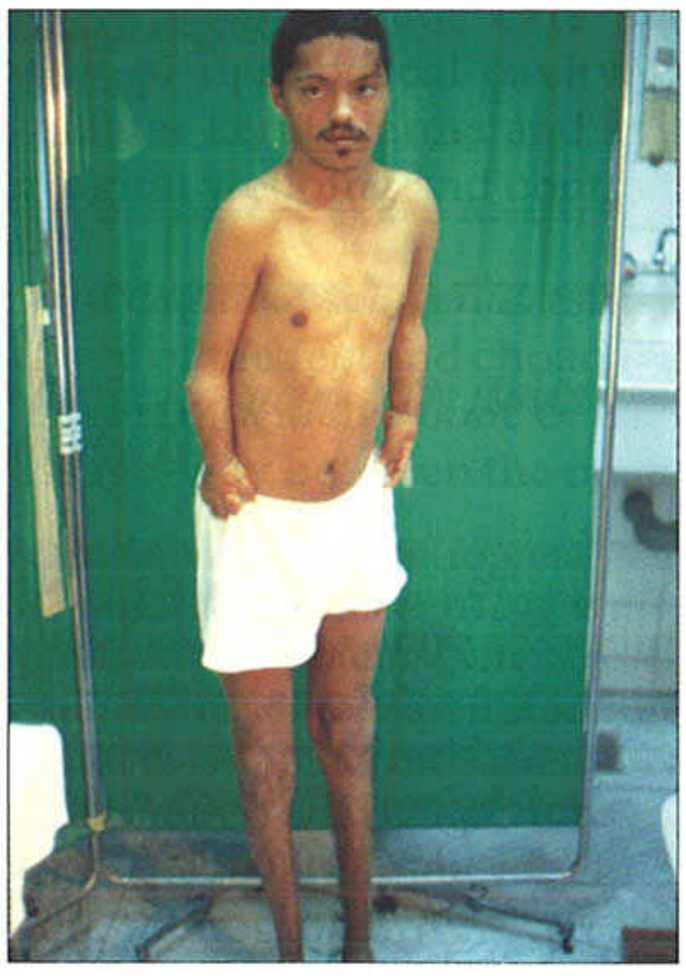


Fig. 12 disproportionate growth with a taller right than left side lower limb

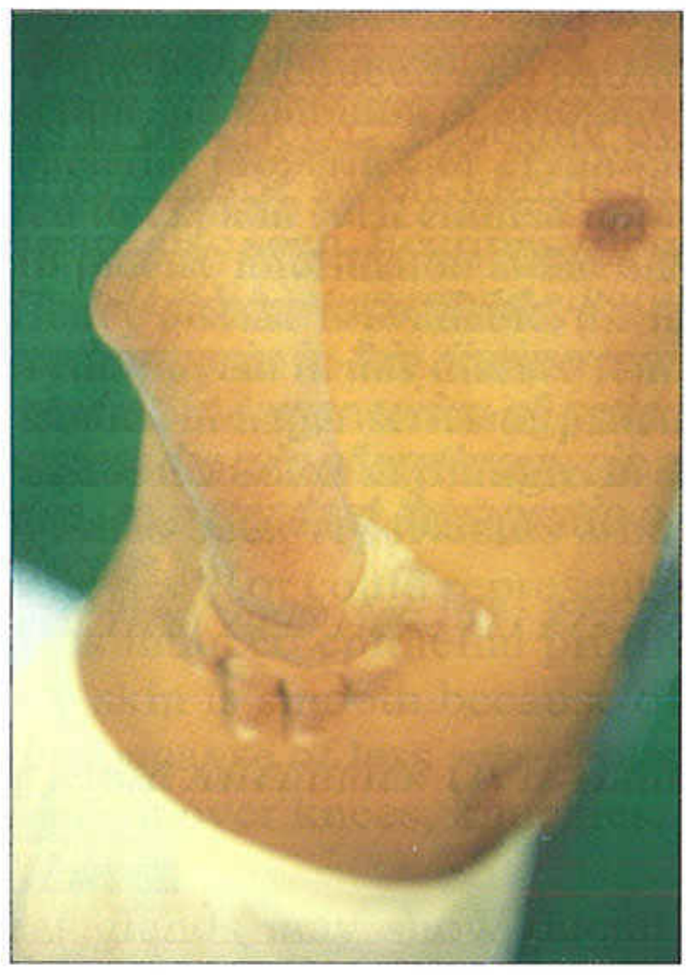


Fig. 13,disproportionate growth of both upper limbs right and left

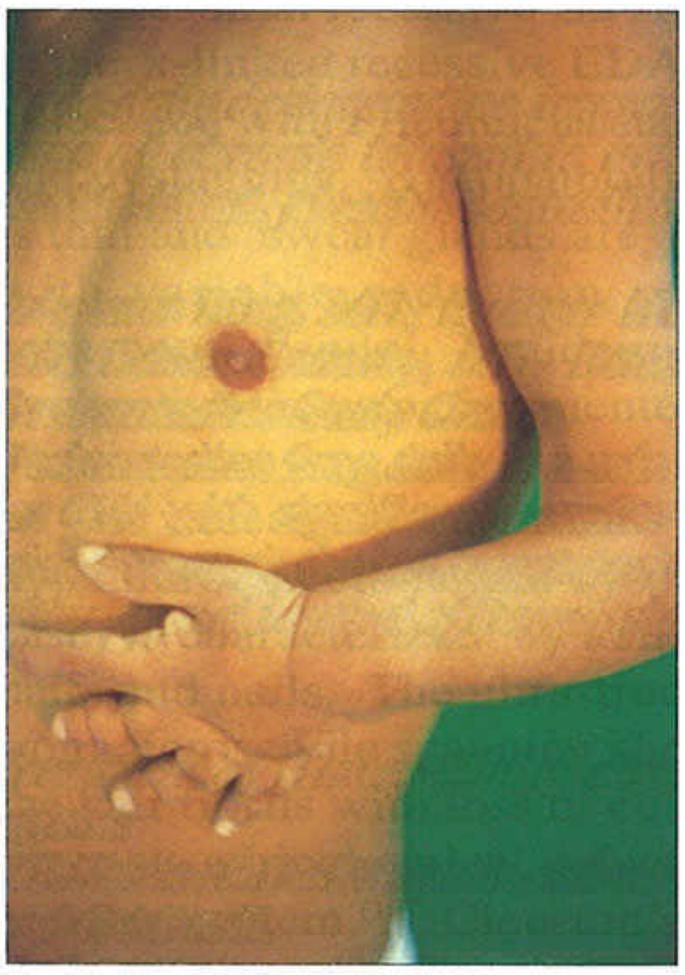


Fig. 14 disproportionate growth of both upper limbs right and left

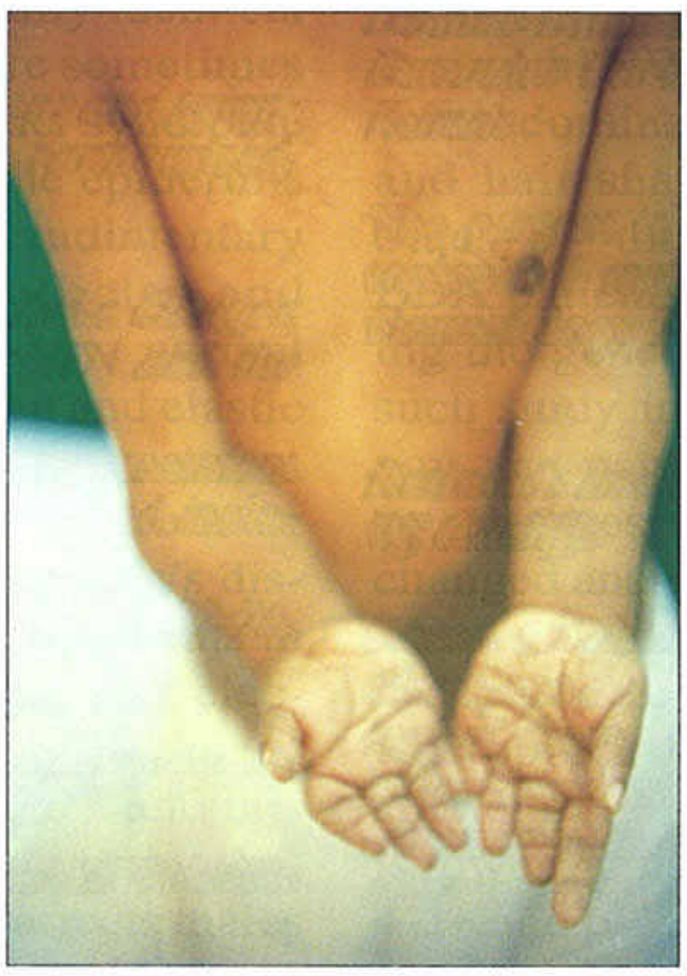


Fig. 15 widely separated nipples

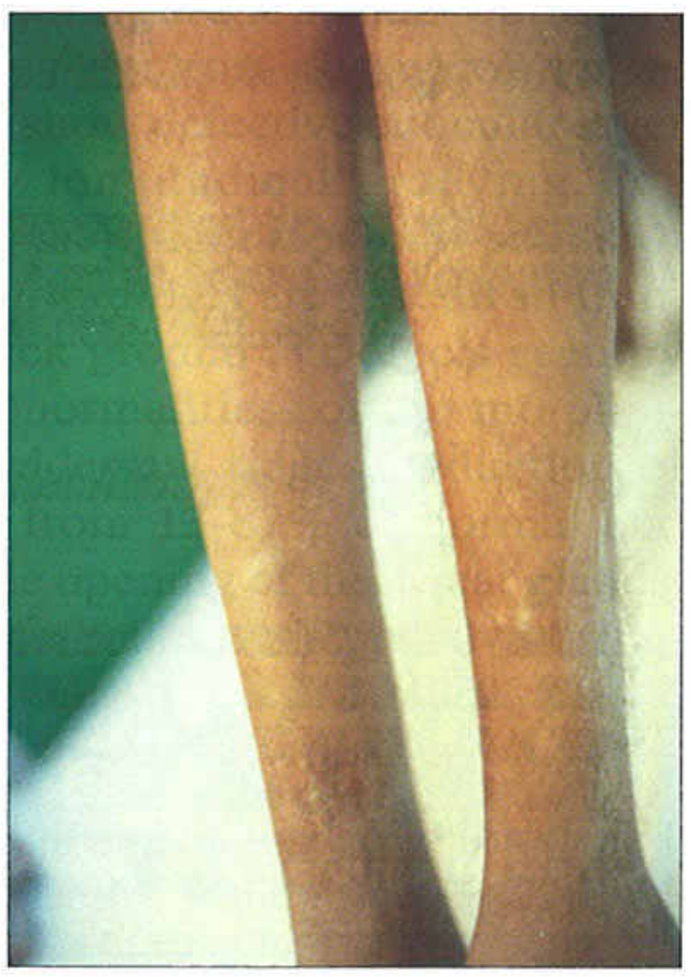
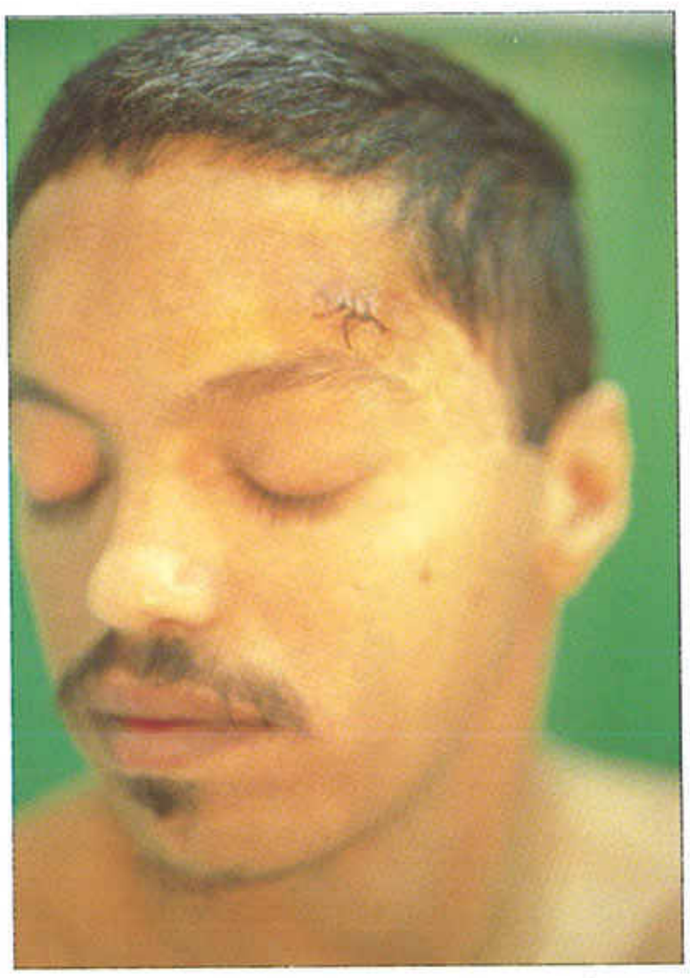


Fig. 16 relatively thin legs.



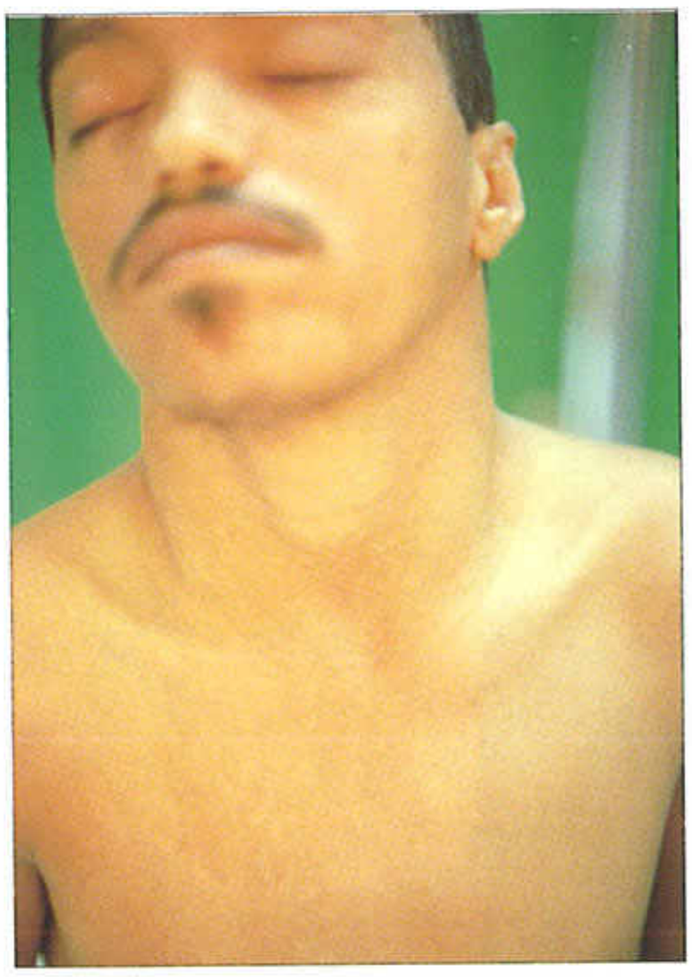


Fig. 17, 18 hypogonadal features and smooth skin with hypotrichosis

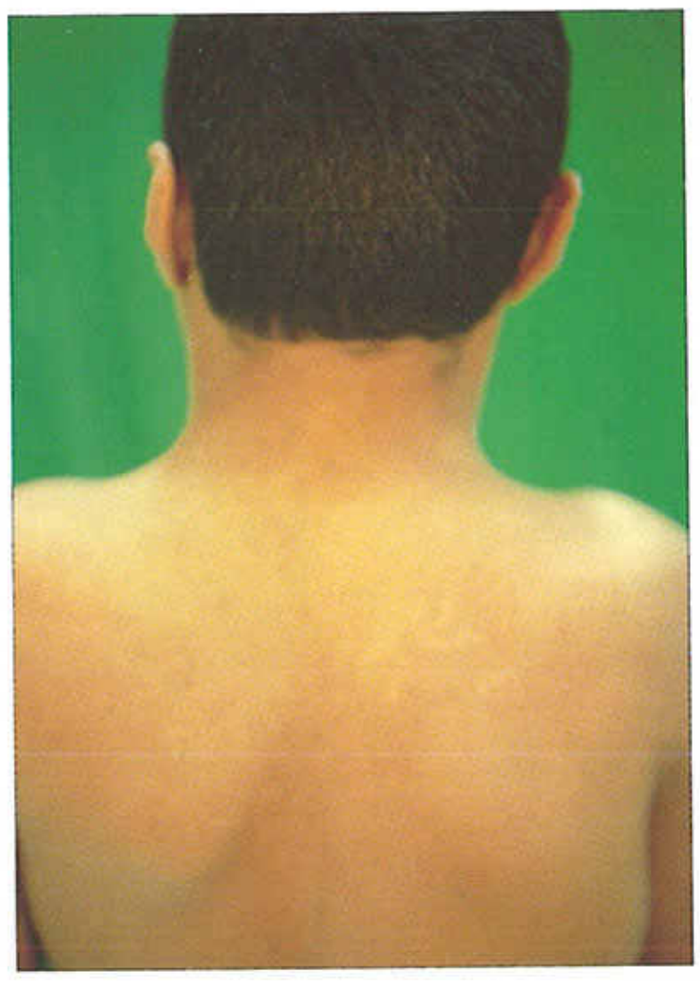


Fig. 19 webbed neck

fied in more than half of the reported cases and included partial or complete hemi-hypertrophy, macrodactyly, plantar or palmer masses of connective tissue nevus or lipomatosis, exostosis affecting cranium or lower limbs, linear or whorled epidermal nevus, scoliosis, lipomatosis including pelvic lipomatosis, hamartomas, cavernous hemangiomas, lymphongiohemangioma, lipoangioma, lymphohemangiomatosis, hamartomas, lipolymphohemangioma.

The associated clinical findings as tabulated by Samlaska [3] included cutaneous findings such as varicosities, decreased subcutaneous tissue, venous prominence, depigmentation, Café au lait macules, angiokeratomas, connective tissue nevus, absent breast, neurofibroma, fibroma. The skeletal associations recorded were macrocephaly, increased growth rate, genuvalgus, long neck, elbow ankylosis, kyphosis, pectus excavatum, retarded bone growth, widely splayed toes, dislocated hip. The craniofacial findings included strabismus, eye defects, malocclusion, arched palate, small occipitofrontal circumference, mandibular prognathism, depressed nasal bridge, low set ears.

The miscellaneous findings were mental retardation, muscle atrophy, prominent abdomen, cystic lung anomalies, seizers, precocious breast development, muscular legs, vocal cord nodule, penile hypertrophy and beaked nose. The case currently reported has seven of the major findings namely cerebriform soles and palms, macrodactyly decreased subcutaneous tissue, inequality of growth of lower limb, arched palate and mental retardation.

The rest of the findings in this case were not listed among the 56 manifestations tabulated by Samlaska et al [3] and these are: crumbled toes and deformed feet, disproportionate growth of limbs, hands, fingers and toes widely separated nipples, webbed neck and hypogonadal features with smooth hypotrichotic skin.

In order to confirm the data regarding the commonly reported clinical manifestations of PS we reviewed 47 articles, which report 52 cases of PS and syndromes sharing some PS manifestations. Six out of 52 cases were encephalocranio-cutaenous lipomatosis (ECL) which may be considered a circumscribed or localized form of PS [9,10] or may be distinct from PS though sharing some clinical manifestation or some of ECL may have manifestations of both ECL and PS [11, 12]. These six cases are excluded from our data. We included in this review case of elephant man. There is evidence suggestive that the historic Elephant man was not a case of neurofibromatosis but a case of PS [13,14]. Males and fe-

males were equally affected. The clinical findings of the 46 proven cases of PS plus the present case (i.e. total of 47 are in the following order of frequency). (as in the table below)

The total number of different clinical manifestations reported are about 70. Each PS patient shows an average of five clinical findings. Our case shows about fourteen clinical signs among which are the new findings of crumbled toes, web neck, hypotricosis and hypogonadal features. The top most clinical criteria of PS as found in the present review are the cerebriform thickening of soles and palms, hemihypertrophy, macrodactyly, asymmetric macrodactyly, epidermal nevus, subcutaneous masses, dermal hypoplasia, lipomatosis, mental retardation, scolosis, lymphangioma, hypopigmented macules, uneven lower limbs and epilepsy. These findings comply with what was found by Samlaska[3]. We stress the characteristic and diagnostic cerebriform thickening of soles and palms in PS although isolated plantar cerebriform callogenoma has been reported and it was suggested that it could be due to Proteus syndrome if somatic mutation occurred later in fetal development [2]. Callogenoma has been found to consist exclusively of collagen type I [29]. The underlying defect seems to be a reduced production of collagenase and a decreased degradation of collagen with enhanced pro-

Clinical finding or deformity	Number of patients	Percentage to who show the deformity	References total reviewed (47)
Cerebriform hypertrophy of soles and or palms	23	49%	3, 4, 15, 16, 17, 18, 19, 20, 21, 22, 23
Hemihypertrophy	13	27.7%	16, 19, 20, 21, 22, 23
Asymmetric macrodactyly and macrodactyly	8	17%	3, 8, 15, 17, 19, 22
Epidermal nevus	8	17%	4, 6, 15, 16, 18, 21, 24
Subcutaneous masses	5	10.6%	17, 18, 19, 22, 25
Dermal hypoplasia	5	10.6%	5, 26
Lipomatosis	4	8.5%	13, 15, 18, 21
Mental Retardation	4	8.5%	16, 24
Scoliosis	4	8.5%	16, 18, 20
Lymphangiomas	3	6.4%	8, 15, 18
Hypaopigmented macules	3	6.4%	4, 6, 19
Uneven lower limbs	3	6.4%	1, 3, 18
Epilepsy	3	6.4%	1, 2, 24
Facial asymmetry	2	4.3%	17, 23
Disproportionate over growth	2	4.3%	23, 26
Exostoses	2	4.3%	27, 28
Port wine stain	2	4.3%	19, 22

Clinical finding or deformity	Number of patients	Percentage to who show the deformity	References total reviewed (47)
Hemangioma	1	2%	18
Angiokeratoma	1	2%	22
Absent superficial femoral v	1	2%	22
Epidermal cyst	1	2%	2
Venous varicosity	1	2%	15
Polydactyly	1	2%	21
Partial lipohypoplasia	1	2%	26
Precocious breast development	1	2%	19
Rhinophyma	1	2%	13
Syndactyly	1	2%	21
Hyperpigmented Lesions	1	2%	4
Exostosis	1	2%	27
Decreased subcutaneous tissue over face and chest	1	2%	3
Cranial hemihypertrophy	1	2%	24
Cranio synostosis	1	2%	28
Patchy decalcification and thinning of cortical layer of long bones	1	2%	28
Epiblepharon	1	2%	28
Endotropy	1	2%	28
Blue sclera	1	2%	28
Telecanthus	1	2%	28
Talipus equines	1	2%	28
Hemimegaly of optic nerve	1	2%	28
Occipital demyelination and compression of corpus callosum	1	2%	28
Cystic bony lesions	1	2%	27
Fibromatoses lesions	1	2%	27

Clinical finding or deformity	Number of patients	Percentage to who show the deformity	References total reviewed (47)
Unilateral tonsillar hypertrophy	1	2%	27
Cholesteatoma	1	2%	27
Hyperplasia of mandible on left side of face	1	2%	27
Genovulgam	1	2%	3%
Atrophy of intestinal villi	1	2%	18
Disproportionate over growth	1	2%	26
Dysmorphic growth with functional orthopedic and orthognatic disabilities that increase with age	1	2%	23
Hydrocephalus	1	2%	16
Protruberance of skull	1	2%	16
Macrocephaly	1	2%	17
Kyphosis	1	2%	17
Nodule of vocal cord with hoarse voice	1	2%	3
Hamartoma of posterior segment of the age	1	2%	7
Venous varicosity	1	2%	15

liferation capacity of the fibroblasts in the lesion contributing to accumulation of collagen [29].

The PS has been confused with overgrowth disorders such as Klippel-Trenaunay-Weber Syndrome[19] neuroflbromatosis, Mafucci syndrome and Bannayan syndrome[7]. Encephalocraniocutaneous lipomatosis syndrome (ECCL) which is a congenital hamartomatous disorder characterized by unilateral skin lesions, lipomas and ipsilateral ophthalmological and cerebral

malformations and the disorder is thought to represent a localized form of PS[9, 10, 11]. PS and ECCL are considered by others to represent distinct entities [12].

The epidermal nevus associated with proteus syndrome is flat, velvety and non organized and is to be differentiated from other epidermal nevus syndrome manifestations[30]. PS, ECCL and epidermal nevus syndrome have several over-lapping phenotypic features and may represent a photypic continuum thus suggesting a common pathogenic process which could be somatic mutation leading to variable patterns of mosaicism [31] and always occur sporadically [32].

Patchy dermal hypoplasia is generally best felt than seen and may be wide spread and result in prominent appearance of veins in affected area. This patchy dermal hypoplasia have been reported to be characteristic of PS[15]. These prominent veins should not be confused with telangiectatic nevi seen in PS[33]

or with the varicose veins in Klippel-Trenaunay-Weber syndrome[34]. Patchy dermal hypoplasia seen in PS is different from Focal dermal hypoplasia (Goltz Syndrome) where the hypoplasia is not patchy but characteristically follows the lines of Blaschko and tend to show herniation of fatty tissue and affects females (88%) being x-linked dominant and appears only in 10-15% of males[35,36]. The paradoxical presence of patchy hypoplasia together with dermal hyperplasia which both characterize PS is explained by genetic concept of twin spotting[15]. At the gene locus PS the embryo would carry one allele giving rise to dermal over growth (Pleioproteus allele-from Greek Pleion meaning plus) whereas the corresponding allele would be responsible for a diminished proliferation of cutaneous fibroblasts (ellatioproteus allele-from Greek elatton, meaning minus) at an early stage of embryogenesis when somatic recombination would give rise to two different populations of cells homozygous for either allele [26].

PS appears sporadically and is postulated to be due to the action of a lethal gene surviving by mosaicism. Cells bearing the mutation can survive only in mosaic state in close proximity to normal cells. The somatic mutation in PS occur early from somatic mutation after fertilization during early embryogenesis [37,38,39]. The mosaicism explains the scattered and asymmetrical distribution of cutaneous lesions and other organs according to the random distribution of the mutant pupulation of cells in soft tissue, viscera, brain and bone.

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