Proteus Syndrome:  
A Case Report of General and Ophthalmic Findings

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Abstract

An 18-year-old girl fulfilled the diagnostic criteria for the Proteus syndrome (PS). Here we report our findings in comprehensive general physical and ocular examination and review the literature focused on clinical manifestations and differential diagnoses. The patient had ‘mild’ involvement of the ophthalmic apparatus: absent foveal reflex, cataract, and abnormal retinal vessels, which in the context of similar reports on ocular manifestations is an indication of wide polymorphism of the condition. Dermatologists, geneticists, and ophthalmologists should be aware of this disorder when they are consulted for the diagnosis of hamartomatous dysplasia conditions.

Keywords: Proteus Syndrome, Absent Foveal Reflex (Macular Hypoplasia), Cataract, Abnormal Retinal Vessels

Introduction

Proteus syndrome (PS) was originally defined as a distinct entity by Cohen and Hayden in 1979, and named after the Greek god, Proteus, by Wiedemann et al in 1983.1 According to Random House Webster’s dictionary, in classic mythology Proteus is ‘a sea god noted for his ability to assume different forms and to prophesy’. This hamartoneoplastic disorder is highly variable and appears to manifest in a mosaic manner.2 It is a complex disorder comprising malformations and overgrowth of multiple tissues giving rise to regional giantism, lymphangiomatous hamartoma, and other variable features including ocular abnormalities.1,3 The cardinal features of the disease are regional overgrowth, hyperostosis, connective tissue and epidermal nevi, and vascular malformations (subcutaneous tumors).2 Manifestations are usually present at birth which become more apparent with time.1,4

The syndrome is probably caused by a sporadic somatic mutation of an autosomal dominant gene during embryogenesis. Somatic nature of the mutation allows survival in an otherwise lethal mutation and its very cause of mosaic presentation and the wide phenotypic variation observed1 involving dysplasia of all three germ layers.3 This variability among and within patients has led to diagnostic confusion and possibly overdiagnosis; reports in the literature have included some patients who have a number of other conditions.2
Our purpose is to report the general and ocular manifestations in a patient with the PS.

**Case Report**

The patient, an 18-year-old girl was referred by a dermatologist for an ophthalmic examination. She was the product of a normal full-term pregnancy and delivery in northeast Iran. There was no parental consanguinity or remarkable family history. Her parents found red lesions on her upper and lower limbs at birth. At one year of age, her parents noticed the asymmetric growth of her limbs; right side grew more than the left, and it proved to be progressive. Signs and time of puberty were normal. She finished school without difficulty.

On our visit, her complaint was red skin lesions on the limbs and asymmetric growth; she had no ophthalmic symptoms.

On physical examination, her right leg was larger than the left, specially distally. She had macrodactyly in her fingers and toes (Figure 1). Multiple red lesions with discrete borders of about 3-4 cm in diameter were observed on the anterior left forearm and leg which disappeared with pressure. A verrucous lesion with a papillomatous appearance was present on her back (Figure 2). Mild kyphoscoliosis was detected on the musculoskeletal examination. Head examination showed a low depressed nasal bridge, philtrum hemangioma, and malocclusion (Figure 3).

Her best corrected visual acuity (BCVA) was $20/25$ for both eyes. Her cycloplegic refraction was $+0.25-0.25\times180$ in the right and $+1.25-0.5\times180$ in the left eye. Visual acuity had no change with cycloplegic correction. Visual field examination (central, 30 degree, static) and ocular motility were normal. The lids, conjunctiva, sclera, cornea, iris, and pupils were normal bilaterally, and there were no iris hamartomas (Lisch nodules). She had palpebral epicanthal folds (supraciliaris type). No epibulbar tumors could be found, and there was no corneal dellen. There was no relative afferent pupillary defect. In slit-lamp biomicroscopy, the anterior chamber, anterior vitreous, and angles were unremarkable except for mild bilateral posterior subcapsular cataracts. Intraocular pressure was 13 mm Hg in both eyes. On fundus exam, disks were normal in appearance and cup/disk ratios were 0.3. Both eyes had absent foveal reflex (macular hypoplasia). Retinal arteries had abnormal branching and retinal veins were dilated in inferior and nasal quadrants and narrowed in superior and temporal quadrants in both eyes. Retinal fluorescein angiography was normal in early and late phases (Figure 4).

![Figure 1. Macrodactyly and ‘disorganization’ of fingers and toes and epidermal nevus](image-url)
Electrocardiogram showed inverted T-waves in inferior leads. Echocardiography revealed mild mitral and pulmonary regurgitation. Radiographic studies reflected the physical findings; the scoliosis was seen, chest x-ray was normal otherwise. Skull x-ray did not reveal asymmetry or exostoses.

**Discussion**

The extreme variability in PS presentation has caused some diagnostic confusion and at times misdiagnosis. Table 1 summarizes general and ophthalmic manifestations reported in the seven articles we reviewed.\(^1\)\(^-\)\(^7\) The intention is not to give frequency or relative significance of these findings. The First National Conference on PS for Parents and Families was held at the National Institutes of Health in Bethesda, Maryland from March 18 to March 20, 1998. Participants developed a set of criteria for the diagnosis of this syndrome. This has been reviewed by Biesecker.\(^2\) Table 2 presents these criteria. Our patient fulfilled the mandatory general criteria and displayed some of the specific criteria.

Differential diagnosis is with a rather lengthy list of congenital hamartoma syndromes associated with vascular malformations and soft tissue/skeletal overgrowth (lipomatosis and pigmentation).\(^1\)\(^-\)\(^4\),\(^7\)\(^-\)\(^9\)

Regarding ophthalmic manifestations, our report is a replication of some of the previously reported findings: macular hypoplasia (absent foveal reflexes),\(^5\) cataract\(^1\),\(^10\),\(^11\) and abnormal retinal vasculature.\(^1\),\(^4\),\(^5\) Becker et al reported a case with numerous eye manifestations.\(^5\) It seems that ophthalmic manifestations can range from minimal or non-existent to overtly manifest, pointing to wide polymorphism as in general findings. Two articles have presented reviews on ophthalmic findings.\(^5\),\(^12\)

According to two of the reviews on the syndrome, frequent misdiagnosis (lack of diagnostic criteria), lack of longitudinal data on natural history, and inadequate attention in the literature to the management of these children are the major problems requiring resolution in PS.\(^2\),\(^3\) A practical account of the natural history, clinical evaluation, surgical management, and psychological counseling with these children (and their parents) has been presented.\(^3\) High resolution chest CT and abdominal and cranial MRI for
assessment of pulmonary cystic malformations, lipomas, and CNS anomalies, respectively, chromosome analysis, and specialist consultations (including dermatological, pediatric, genetic, and orthopaedic) are among the suggested interventions. Patients can also be referred to PS Foundation which is established to support and educate families and professionals and to raise funds for research on the disease.\textsuperscript{13}

Table 1. Manifestations reported in Proteus syndrome

| Manifestations                                           | Regional giantism or disproportionate overgrowth | Depressed/low nasal bridge | Linear hyperpigmentation | Epidermal nevus (linear), plantar or palmar cerebriform/gynoid hyperplasia | Connective tissue nevus | Pulmonary cystic malformations | Vascular malformations: capillary (hemangioma), venous, lymphatic | Lymphangioma (subcutaneous, deep) | Unilateral angiectasia of the thoracic cord | Scoliosis | Lower extremity varicosity | Ovarian cyst (bilateral) | Ovarian cystadenoma (bilateral) | Parotid monomorphic adenoma | Lipoma: intra-abdominal, intra-thoracic, superficial (subcutaneous) | Joint deformities/dislocations | Regional subcutaneous fat deficiency | Macrophthalmia | Conjunctival capillary hemangioma | Epibulbar tumor or cystic lesions | Heterochoroma irides | Anisocoria | Scotomas | Hamartoma of the lids | Strabismus | Nystagmus | Ptosis | High myopia | Astigmatism | Esotropia | Downslanting of palpebral fissures | Posteri segment hemartoma | Glaucoma | Cataract | Calific band keratopathy | Retinal coloboma | Retinal detachment | Retinal pigmentary abnormalities | Latice degeneration | Absent foveal reflexes and/or foveal hypoplasia | Retinal gliosis | Retinal pits | Serous retinal detachment | Drusen of optic disc | Tortuosity of retinal vessels | Decreased arteriolar caliber | Dilated vessels | Pale optic disk | Chorioretinal hamartoma |

Table 2. Diagnostic criteria for Proteus syndrome

<table>
<thead>
<tr>
<th>General criteria (mandatory)</th>
<th>Mosaic distribution of lesions</th>
<th>Progressive course</th>
<th>Sporadic occurrence</th>
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<tbody>
<tr>
<td>Specific criteria (category signs)</td>
<td>A. Connective tissue nevus</td>
<td>B. 1. Epidermal nevus</td>
<td>2. Disproportionate overgrowth</td>
</tr>
</tbody>
</table>

Diagnosis can be made in the presence of ALL mandatory criteria TOGETHER with certain category signs: one sign from A OR two from B OR three from C.

Taken for Venugopalan et al\textsuperscript{7} [modified from Biesecker et al\textsuperscript{2}]

Conclusion

Finally, dermatologists, geneticists, and ophthalmologists in particular should be aware of this disorder whenever they are consulted for hamartomatous dysplasia conditions.

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References