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PROTEUS SYNDROME

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Proteus syndrome is a disorder of segmental or mosaic overgrowth that can affect any tissue. The most common complications include overgrowth that can lead to orthopedic complications, soft tissue overgrowth of the feet, linear nevi, vascular malformations, and tumor predisposition. All confirmed cases are sporadic, and it has been hypothesized that the disorder is caused by a postzygotic mutation in a growth-promoting gene. Proteus syndrome is rare and overdiagnosed. There are fewer than 100 documented cases in the literature, and many people who carry the diagnosis cannot be confirmed as affected when published diagnostic criteria are rigorously applied.

INTRODUCTION

Proteus syndrome is a disorder of segmental or mosaic overgrowth that can affect any tissue. The most common complications include overgrowth that can lead to orthopedic complications, soft tissue overgrowth of the feet, linear nevi, vascular malformations, and tumor predisposition. All confirmed cases are sporadic, and it has been hypothesized that the disorder is caused by a postzygotic mutation in a growth-promoting gene. The syndrome was delineated by Cohen and Hayden (Cohen and Hayden, 1979) and was named by Wiedemann (Wiedemann et al., 1983). The earliest known case was published in the nineteenth century by Treves (Treves, 1885; Cohen, 1987).

Incidence

Proteus syndrome is rare and overdiagnosed. There are fewer than 100 documented cases in the literature, and many people who carry the diagnosis cannot be confirmed as affected when published diagnostic criteria (Biesecker et al., 1999) are rigorously applied.

Diagnostic Criteria

There has been substantial confusion about the diagnosis of Proteus syndrome. This was first recognized at a gathering of 18 affected individuals at the National Institutes of Health in 1998 (Biesecker et al., 1998). At this meeting, it was clear that the individuals who carried this diagnosis were heterogeneous. A number of those affected had primarily postnatal onset of overgrowth with aggressive, irregular, and disproportionate hyperplasia; progressive bony distortion; venous, capillary, and lymphatic vascular malformations; connective tissue nevi of the feet; and linear verrucous epidermal nevi of the skin. These distinct manifestations and natural history are consistent with the original description and warrant the diagnostic label of Proteus syndrome. Subsequently, diagnostic criteria were devised and are summarized in Table 37.1. While the authors of these criteria have found them useful for research and for counseling and managing individuals, substantial confusion persists. In the National Institutes of Health Proteus syndrome research program, most individuals referred with a diagnosis of Proteus syndrome are rediagnosed with another condition upon application of the diagnostic criteria. Although it may be argued that these criteria are excessively strict and that Proteus syndrome may be part of a continuous spectrum, the careful use of these criteria reliably divides individuals into a progressive, high-risk group (Proteus syndrome) and a static, low-risk group (hemihyperplasia, see below) (personal experience).

It is imperative to understand the intent of each of the criteria as outlined in Table 37.1. Progressive overgrowth in Proteus syndrome is almost always relentless and, in most cases, severe. It should not be confused with the growth of a lipoma in a person with hemihyperplasia. Severe overgrowth will occur in areas of the body that were entirely normal at birth. Another critical feature of the overgrowth seen in Proteus syndrome is its irregularity, leading to distortion of cutaneous, subcutaneous, cartilaginous, and bony tissues. In contrast, the overgrowth seen

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TABLE 37.1 Diagnostic Criteria for Proteus Syndrome[a]

General Criteria: Mosaic distribution AND Progressive course, AND sporadic occurrence
Category A: cerebriform connective tissue nevus
Category B
1. Epidermal nevus
2. Disproportionate overgrowth of two of: limbs, skull, external auditory canal, vertebrae, or viscera
3. Bilateral ovarian cystadenomas or monomorphic adenomas of the parotid gland in childhood

Category C
1. Dysregulated adipose tissue (either lipoatrophy or lipomas)
2. Vascular malformations: capillary, venous, or lymphatic
3. Facial phenotype: long face, dolichocephaly, down-slanted palpebral fissures, low nasal bridge, wide or anteverted nares, open mouth at rest

[a]To make a diagnosis of Proteus syndrome requires all three general criteria plus either one from A, two from B, or three from C.

Source: Adapted from Biesecker et al. (1999).

in hemihyperplasia is highly regular, a "ballooning," resulting in a body part that is large but easily recognizable. In general, upon radiographic examination, the bones underlying these enlarged body parts in hemihyperplasia are enlarged but are normal in structure. In contrast, in Proteus syndrome, bony and cartilaginous structures are distorted, sometimes beyond recognition.

A second critical feature of Proteus syndrome is the connective tissue nevus, also known as a cerebriform lesion or moccasin lesion when present on the sole of the foot, which is common. While many individuals with Proteus syndrome may not have this lesion, when present, it is very helpful for making the diagnosis. However, there is confusion regarding this sign as well. This lesion is caused by hyperplasia of the cutaneous and subcutaneous tissues with thickening of more than a centimeter. This overgrowth is irregular, leading to marked thickening adjacent to deep furrows, which may resemble the surface of the brain. This was the genesis of the term *cerebriform hyperplasia.* This tissue is much firmer than the corresponding tissue that it replaces. Although this lesion is most common on the soles, it can also occur on the hands, perinasal area, or near the canthus.

The specific diagnostic criteria in categories A, B, and C (see Table 37.1) are accompanied by three general diagnostic features that must all be present. First, the overgrowth must be patchy or mosaic. There are no individuals with Proteus syndrome who have evenly distributed overgrowth, and this manifestation is predicted not to occur by the etiological model below. Second, the occurrence must be sporadic, as there are no confirmed familial cases; again, this is thought to be impossible by the pathogenetic model of the disease. Third, all cases must be progressive, as defined above. These general criteria are based on the mosaicism model below, which has so far proven to be remarkably useful for understanding this disorder.

Finally, it must be mentioned that a former name for Proteus syndrome is "Elephant man disease," after the book and movie of the same title describing the life of Joseph Carey Merrick who lived in England from 1862 to 1890. Mr. Merrick's medical condition was described in detail by his surgeon (Treves, 1885), and good evidence has been presented to show that Mr. Merrick was affected with Proteus syndrome (Cohen, 1987). However, he was affected to a severe degree, and the many negative connotations affiliated with that story are either not useful or even harmful to those who are affected by the disorder. Therefore, the use of that pejorative diagnosis is discouraged.

Etiology, Pathogenesis, and Genetics

In all confirmed cases of Proteus syndrome described to date, the individuals were affected in a patchy or mosaic pattern and were sporadic. The disorder is pan ethnic and there are no data to suggest any differences in frequency among the major ethnic groups. Interestingly, there have been two cases of monozygotic twins who are discordant for the disorder (although the diagnoses have not been independently confirmed in these cases). These observations have been used to generate a model of Proteus syndrome (Happle, 1987). This model proposes that Proteus syndrome is caused by a postzygotic mutation in a gene that causes deregulation of growth in the daughter cells of that lineage. Furthermore, the model proposes that the mutation, if present in all cells, would be lethal at an early stage of development, or perhaps even in the gamete. Thus, affected persons have only unaffected children. At least three affected adults have had four pregnancies, all of which were unaffected. This model is likely relevant to an entire class of disorders such as hemihypertrophy with multiple lipomatosis, Klippel-Trenaunay syndrome, and the McCune-Albright syndrome. Although the gene mutated in McCune-Albright syndrome is known, the germline lethality hypothesis is not formally proven for proteus syndrome. It is hypothesized that each of these disorders is caused by mutations in distinct genes, but in mosaic form.

Much confusion has been generated surrounding the issue of mutations of the gene *PTEN* in Proteus syndrome. Some individuals with *PTEN* mutations are claimed to have Proteus syndrome or "Proteus-like syndrome," the latter being a designation that engenders little clarity (Zhou et al., 2001; Smith et al., 2002). These reports have been reviewed, and it has been concluded that there are either insufficient data to diagnose Proteus syndrome or, when the data are sufficient, it is clear that the diagnosis is wrong. We suspect that there are some individuals with *PTEN* mutations who have overgrowth syndromes (such as Bannyan-Riley-Ruvalcaba syndrome or less distinct patterns of overgrowth) that can be confused with Proteus syndrome. However, astute clinicians recognize the importance of careful phenotypic evaluations and thoughtful application of recognized diagnostic criteria.

Diagnostic Testing

There are no known molecular or biochemical tests that are useful in individuals who meet the clinical diagnostic criteria described above. Those who do not meet these criteria may have one of a number of overlapping disorders of somatic overgrowth

(see below). In those cases, appropriate molecular testing, such as *PTEN* sequencing, may be considered.

Differential Diagnosis

The most common disorder that should be considered in a person with segmental overgrowth is hemihyperplasia with multiple lipomatosis (Biesecker et al., 1998) and other forms of hemihyperplasia (Cohen et al., 2002a). The majority of individuals referred to the National Institutes of Health for the Proteus syndrome study have been rediagnosed with hemihyperplasia with multiple lipomatosis on review of records, clinical photographs, and plain radiographs. The main features that distinguish hemihyperplasia with multiple lipomatosis from Proteus syndrome are nonprogressivity (the overgrown limb grows in a commensurate manner to the rest of the body), capillary vascular malformations, and lipomas. The overgrowth in hemihyperplasia with multiple lipomatosis is typically described as "ballooning," whereas in Proteus it is distorting. In general, the prognosis of hemihyperplasia with multiple lipomatosis is less grave than that of Proteus syndrome, although there is a potential association with Wilms tumor and hepatoblastoma. Typical hemihyperplasia is not progressive, which means that most affected individuals are born with asymmetry and, as they grow, the asymmetry stays proportionate and is commensurate with the overall growth of the child throughout life. In any case, isolated hemihyperplasia is a manifestation of overgrowth, not a diagnosis (Cohen et al., 2002a). Klippel-Trenaunay syndrome consists of capillary, venous, and lymphatic vascular malformations (sometimes these malformations are mixtures of vessel types), with overgrowth that is typically in the same segment as the vascular malformation (Cohen et al., 2002b). The bones in overgrown segments are enlarged but not typically distorted, and the affected individuals do not have hyperostoses, or connective tissue or epidermal nevi. Maffucci syndrome is defined as multiple enchondromatosis with vascular malformations, and the former is sometimes confused with hyperostosis (Cohen et al., 2002c). Maffucci syndrome has no other overlap with Proteus syndrome.

MANIFESTATIONS AND MANAGEMENT

It must be borne in mind that Proteus syndrome is a very rare disorder and experience is limited. The National Institutes of Health series of 35 affected individuals is the largest in the world, yet it is an inadequate sample from which to draw clear conclusions or make firm recommendations for management of all cases. The disorder is usually severe and affects many body systems; therefore decisions about treating any one body system nearly always involve considerations of many other involved body systems. Effective management generally requires a large and diverse team of medical specialists willing to invest time to make thoughtful decisions about diagnosis and treatment.

Growth and Feeding

Growth issues can be challenging in Proteus syndrome. Most affected individuals have severe asymmetric overgrowth that can cause leg length discrepancy (in one case more than 15 cm). Many persons have a lipodystrophy that includes lipomas or lipomatous infiltration of muscles and viscera in some parts of the body and lipoatrophy in other parts of the body. Some affected individuals also have significant undergrowth of some muscle groups, the upper extremities being most often involved. There is no known biochemical or hormonal explanation for this observation, although it has not been investigated rigorously. It has been claimed that Proteus syndrome "burns out" with adolescence insofar as some individuals seem to experience a cessation or marked diminution of their overgrowth near the end of puberty. While this is not universal, it may be common, and this consideration is critical for planning treatment.

Evaluation

- Apparent failure to thrive should be investigated in a standard manner.

Treatment

- Feeding excess calories does not appear to be helpful to treat the underdevelopment or lipoatrophy.
- The use of growth-stimulating or androgenic hormones to treat this manifestation is not recommended because of the unknown effects of such treatment on hyperplastic tissues.

Development and Behavior

Development can be delayed, and a minority of affected individuals are mentally retarded (probably less than 10–15%, although these estimates are problematic because of ascertainment bias.) There are no known stereotypical or common behavioral problems.

Evaluation

- Developmental milestones should be monitored
- If developmental delay is evident and unexplained by structural abnormalities, formal developmental assessment should take place.

Treatment

- Appropriate interventions and therapies, including educational programming, should be instituted, as indicated by the defects identified.

Musculoskeletal

The musculoskeletal manifestations of Proteus syndrome are as common as they are daunting [for review, see Cohen et al. (2002d)]. The relentlessly progressive nature of the disorder and the frequent involvement of bones, cartilage, muscle, and connective tissues cause symptoms in nearly all affected individuals. Most have asymmetric overgrowth that primarily affects the length of the tubular bones but can also affect bone width, joint capsule, connective tissues, and muscles. Lipomatous infiltration of muscle groups can cause an underestimate of the degree of

muscle underdevelopment. More troubling than simple asymmetry of the length of one member of a pair of bony structures is the asymmetric overgrowth within a single bone. One of the most common manifestations of this phenomenon is in the proximal tibia where two sides of a primary epiphyseal growth plate can have markedly different rates of growth, leading to the rapid development of bowing, severe varus, or valgus deformities at the knees. Another common manifestation is hyperplasia of the cartilaginous tissues surrounding the joints (knees and digits most commonly) leading to rapid and, in some cases, nearly complete, loss of joint mobility. A few individuals also have ectopic calcification of tendons and muscles. The axial skeleton can also manifest asymmetric overgrowth of the vertebral bodies leading to rapidly progressive scoliosis and subsequent restrictive lung disease.

Evaluation

- Axial and appendicular skeletal abnormalities are best evaluated by careful physical examination and plain film radiography.
- Computed tomography with three-dimensional reconstruction may become more important when that technique is more widely available.
- Involvement of an orthopedist should occur early, certainly no later than when there is functional impact from overgrowth.

Treatment

- Treatment of overgrowth and asymmetric epiphyseal growth is best managed by epiphyseodesis by curettage or stapling. The timing of these procedures is crucial to effect an appropriate correction of angulation or balancing of growth.
- Osteotomy to reduce bone length may be required if epiphyseal manipulation alone is insufficient. This technique can be used to shorten and/or straighten tubular bones.
- Spinal fusion is indicated for persons who have, or are likely to develop, pulmonary compromise. Bracing may be less effective when there is asymmetric or irregular overgrowth of vertebral bodies. Spinal fusion has been performed successfully in persons with Proteus syndrome using modern surgical techniques. Again, timing is challenging because early correction may avoid complications associated with future worsening of the primary lesions, however, later surgery may be preferred to optimize growth.
- For lesser degrees of leg length asymmetry, shoe lifts are indicated.
- The Ilizarov technique is not generally recommended for the purpose of lengthening of tubular bones, as the shorter bone is generally the normal bone. Avoiding overgrowth of the pathologic bone by epiphyseodesis is strongly preferred.
- Replacement of joints that have lost their mobility (hips, knees, etc.) with prosthetic joints may be useful.
- Any surgical procedure that requires prolonged operating room time or convalescent immobility should raise the consideration of prophylactic anticoagulation (see **Respiratory** section).

Respiratory

Individuals with Proteus syndrome can have primary or secondary pulmonary disease. Secondary complications arise from scoliosis. The primary pulmonary manifestation of Proteus syndrome is cystic degeneration of the lungs (Newman et al., 1994). This manifestation can be asymptomatic but puts affected individuals at risk for pneumonia. Proteus syndrome also predisposes to deep venous thrombosis and pulmonary embolism (Slavotinek et al., 2000). This complication has occurred in children as young as 9 years of age and is a major challenge as most pediatricians are unfamiliar with the diagnosis and management of these problems. The onset of symptoms can be sudden and the outcome catastrophic. It is believed that deep venous thrombosis and pulmonary embolism are major contributors to the early mortality associated with Proteus syndrome. Aggressive management can be effective and should be implemented emergently.

Evaluation

- Symptoms of chronic pulmonary compromise, pneumonia, or the need for major surgical procedures should prompt consideration of high-resolution computed tomography scanning of the chest to exclude cystic malformations. This is the most effective imaging modality for this complication (Newman et al., 1994). Individuals with clinically significant degrees of cystic degeneration should also be considered for ventilation-perfusion scanning.
- The acute onset of pulmonary insufficiency or chest pain in a person with Proteus syndrome of any age should be considered pulmonary embolism until proven otherwise.
- High-resolution chest computed tomography with intravenous contrast is the most effective and rapid diagnostic technique for pulmonary embolism. The classic algorithm of ventilation/perfusion scanning followed by pulmonary angiography may be preferred in some situations, but is more time consuming.

Treatment

- Individuals with cystic degeneration of the lungs but without obvious symptoms need to be monitored for pneumonia and atelectasis. They should be carefully evaluated when they are febrile, as pneumonia is a likely complication due to the poor clearance of secretions from the cystic lung tissue.
- Individuals with pulmonary cystic degeneration should have vigorous pulmonary toilet during postoperative convalescence.
- Individuals with chronic ventilation-perfusion mismatching may be considered for resection of dysfunctional lung tissue, although there is no experience with this treatment.

- The acute onset of symptoms associated with deep venous thrombosis and pulmonary embolism should be promptly and aggressively treated with anticoagulation. Consideration may be given to focal treatment with thrombolytic agents, although their use in Proteus syndrome has not been demonstrated to be safe or effective.
- Following recovery from an acute pulmonary embolism, anticoagulation therapy must be individualized, as there are no data to allow general recommendations for the duration of anticoagulation.
- Chronic anticoagulation and prophylactic anticoagulation are not routinely recommended. The long-term risks and benefits are unknown and must be weighed carefully for each individual. Some individuals may benefit from such therapy, but the risks of anticoagulation may be high in children and in persons with vascular malformations.

Gastrointestinal

Several individuals have had gastrointestinal complications including rectal prolapse and gastric outlet obstruction from hamartomatous gut wall tissue, and numerous individuals have intraabdominal lipomatous infiltration (Lublin et al., 2002). There may be significant gastrointestinal blood loss from hemorrhagic bowel masses. It might be expected that individuals with Proteus syndrome would be at risk for intussusception or acute bowel obstruction secondary to hamartomas or lipomas. Although only a single case has been documented in the past (Costa et al., 1985), it is important to be aware of this potential complication.

Evaluation

- Rectal prolapse should be evaluated by standard imaging modalities such as barium enema and flexible or rigid endoscopy. This manifestation has been associated with hamartomas of the bowel wall, which should be readily identifiable with these techniques.
- Contrast imaging studies such as upper gastrointestinal series with small-bowel follow through or oral contrast computed tomography may be useful if intussusception or acute bowel obstruction is suspected.
- Gastrointestinal blood loss should be excluded in any individual with anemia or melena using standard clinical techniques.
- As in all cases of bowel obstruction, regardless of cause, urgent diagnosis and treatment are critical to avoid complications. In Proteus syndrome, the urgency of relieving obstruction and avoiding bowel perforation must be balanced by an appreciation of the difficulties inherent in operating on individuals who have multisystem disease and who may have markedly abnormal anatomy or lesions that are difficult to resect (e.g., lymphatic vascular malformations). Careful thought should be given to balancing the urgency to operate with the benefits of obtaining a thorough preoperative evaluation by detailed imaging studies and consultations.

Treatment

- Surgical treatment of gastrointestinal lesions in Proteus syndrome should be undertaken with a full appreciation of the peculiar nature of the disorder and the possibility of rare lesions or abnormal anatomy.
- Although it has been claimed that surgery on abnormal tissue activates or aggravates the overgrowth in Proteus syndrome, supporting data are lacking. This concern should not weigh heavily in making a decision about operating on a child with an acute lesion, especially an acute abdomen.

Neurologic

One of the most common central nervous system abnormalities is hemimegalencephaly (enlargement of one side of the brain), which is presumably caused by the same mechanism as the overgrowths in other tissues and organs. Several individuals with Proteus syndrome have been found to have neuronal migration abnormalities, although the frequency and severity of this problem are not well characterized. Seizures are uncommon but, when present, are often associated with hemimegalencephaly or other central nervous system abnormalities. A potentially problematic lesion is hyperostosis of the skull, which is uncommon but can exceed 5 cm in thickness in severe cases. Although this lesion appears to have the potential to cause central nervous system symptoms by cortical compression or distortion, this is not a common problem, as most affected individuals are asymptomatic from a neurologic perspective.

Evaluation

- A full developmental and neurologic evaluation should be carried out at diagnosis and repeated periodically until puberty.
- Computed tomography or magnetic resonance imaging of the brain are effective modalities for imaging. Computed tomography is preferable for imaging the skull and magnetic resonance imaging preferable for the brain. Indications for cranial imaging include significant skull asymmetry or focal overgrowth, neurologic symptoms including seizures or focal neurologic signs on examination, and developmental delay or mental retardation.
- Electroencephalogram is useful for the characterization of potential seizures.

Treatment

- Several individuals who have surprising degrees of hyperostosis and cortical distortion or displacement have shown no apparent signs of neurologic dysfunction (personal observation). For this reason, skull hyperostosis should generally be managed by observation if and until it is clear that the lesion is causing neurologic symptoms.
- There is no treatment for hemimegalencephaly.
- Seizures should be treated symptomatically, as one would in the general population.

Ophthalmology

There have been several reports linking Proteus syndrome to disorders of the globe and surrounding tissues (Bouzas et al., 1993). Epibulbar benign tumors are probably the most common manifestation in the globe, whereas the most common periorbital lesions are hyperostoses and connective tissue nevi. Lesions can occur anywhere in the neuro-optic pathway including physical impingement of the periorbital tissues, compression of the globe by tumors, epibulbar dermoids that expand over the cornea, retinal lesions, compression of the optic nerve or tract by tumors, or lesions of the occipital cortex.

Evaluation

- Thorough evaluation of the optic axis is recommended for any individual with Proteus syndrome and an ophthalmologic complaint.
- Common modalities for evaluation include direct and indirect ophthalmoscopy, electroretinograms, magnetic resonance imaging, or computed tomography of the eye and surrounding structures.

Treatment

- Surgical treatment of lesions that impinge on the optical axis is useful and appropriate. Due to the progressive nature of the disorder, such procedures must be planned carefully because some procedures must be performed repeatedly due to regrowth of a lesion such as periorbital hyperostosis.

Otolaryngology

Several affected individuals have had soft tissue overgrowth of the airway that obstructs respiration. Hyperplasia of the tonsils and adenoids may be common and can be asymmetric. Extrinsic compression of the posterior wall of the pharynx and larynx by hyperostoses of the vertebral bodies has been seen in several individuals. Hyperostosis of the external auditory canal can lead to complete occlusion of the canal and conductive hearing loss.

Evaluation

- Standard modalities of polysomnography, flexible endoscopy, pulmonary function tests, and imaging studies including computed tomography and virtual bronchoscopy may be used when upper airway compression or obstruction is suspected.
- The external auditory canals should be examined periodically to exclude hyperostosis of the external auditory canal.

Treatment

- Hyperostoses of the external auditory canal should be surgically reduced when they impair hearing or cause discomfort.
- Intrinsic lesions of the airway such as hyperplastic nodules that obstruct respiration should be excised.
- The only known treatment for extrinsic compression of the airway from hyperostoses of the vertebra is to bypass the obstruction with a tracheostomy.

Genitourinary

Ovarian cystadenomas are common in Proteus syndrome and should be excised when symptomatic (Gordon et al., 1995). Other hyperplastic lesions of the genital tract have also been encountered. Cystic lesions of the epididymis are common in males, but they appear to be benign. Inguinal hernias are common in Proteus syndrome and may be isolated or associated with lipomas of the inguinal canal.

Evaluation

- When abdominal or pelvic pain is present, a search should be made for ovarian cystadenomas or other tumors, even in young children.
- Ultrasound is the preferred primary imaging tool for the pelvic lesions of Proteus syndrome. Magnetic resonance imaging and computed tomography are also useful.
- Inguinal hernias should be evaluated by ultrasound and exploration.

Treatment

- Surgical excision of ovarian masses is the recommended treatment.
- We recommend monitoring epididymal cystic masses and operating only when they appear to be expansile or have other characteristics of malignancy.
- Repair of inguinal hernias should be accompanied by dissection to exclude lipomas or lymphatic vascular malformations. The latter may be difficult to resect, but resection is nonetheless important because these anomalies may predispose to recurrence.

Dermatologic

Nearly all individuals with Proteus syndrome have some dermatologic manifestations [for review, see Cohen et al. (2002d)]. These can include linear verrucous epidermal nevi, connective tissue nevi, and cutaneous vascular malformations. Connective tissue nevi are especially troublesome as they can cause difficulties with shoe fit, biomechanical changes, and odor.

Evaluation

- An evaluation by a dermatologist is recommended for all individuals with a confirmed or suspected diagnosis of Proteus syndrome. Ongoing care by a dermatologist (or plastic surgeon) may be necessary for those with symptomatic vascular malformations.
- Acutely malodorous connective tissue nevi should be cultured for bacterial and fungal growth.

Treatment

- Skin care should consist of brief bathing with mild nonsoap cleansers and thorough but gentle drying (a hair dryer on low heat works well).
- Moisturizers with minimal fragrances, colors, etc. may be used liberally.
- Malodorous connective tissue nevi need to be cleaned thoroughly but gently, using cotton swabs to cleanse the sulci.
- Aluminum chloride solution may be applied to the feet to reduce perspiration.
- Infections should be treated with appropriate topical or systemic antimicrobials.
- Debulking procedures to treat foot overgrowth have frequent complications, especially if they involve the sole of the foot (usually for a connective tissue nevus).

Cardiovascular

Although cardiac lesions are rare in Proteus syndrome, vascular manifestations are essentially universal. These range from trivial cutaneous capillary vascular malformations to gigantic mixed lesions with capillary, venous, and lymphatic components. Some are also mixed with lipomatous tissue. High-flow or arterial vascular malformations are not common in Proteus syndrome.

Evaluation

- Imaging of vascular malformations other than pure capillary vascular malformations (which do not require imaging) can be accomplished with magnetic resonance imaging, ultrasound, and, in select cases, invasive studies such as lymphangiography.

Treatment

- Treatment of the most common lesion of Proteus syndrome (the mixed lymphatic-venous-lipomatous malformation) should be reserved for cases where the lesion interferes with function or has major cosmetic or disfigurement implications.
- Surgery is the preferred treatment for these lesions. However, it should be borne in mind that dissection of malformations that include lymphatics may be challenging and postoperative weeping from the margins is common.
- Laser treatment is unlikely to be beneficial for these lesions, although hemangiomas that may occur in Proteus syndrome may respond to laser treatment.

Neoplasia

It is recognized that individuals with Proteus syndrome have experienced a number of unusual tumors and that the rarity of these tumors in the general population strongly suggests (but does not prove) that tumor predisposition is part of the disorder (Cohen et al., 2002d). However, the wide variety of tumors and the disparate location of those tumors make screening difficult, and the efficacy of such screening is unknown. Instead of routine screening, prompt and vigorous evaluation of signs or symptoms of malignancy is recommended.

Evaluation

- In lieu of screening, affected individuals with any signs and symptoms of a malignancy should be promptly and thoroughly evaluated for a tumor. Because of the wide variety of tumors, specific recommendations cannot be made, and physicians instead must use clinical judgment to prompt such evaluations.

Treatment

- Aggressive treatment of tumors (surgery, irradiation, and chemotherapy) is indicated, as there are no data to suggest that tumors in Proteus syndrome have a worse prognosis than in the general population.

Endocrine

Little is known about the involvement of the endocrine system in Proteus syndrome. One person has been reported with goiter (Viljoen et al., 1987), although it is not known if this is causally related to the underlying diagnosis of Proteus syndrome.

Evaluation

- A suspicion of thyroid disease should prompt thyroid function tests.

Treatment

- Under- or overactivity should be treated in a standard manner.

Dental

Dental abnormalities are common in Proteus syndrome due to asymmetric overgrowth of the mandible and maxilla. Some individuals have enlarged or malformed teeth.

Evaluation

- Physical and radiographic examination by an orthodontist may be useful when it is clear that dental malalignment is developing.

Treatment

- Orthodontic treatment may be appropriate for some individuals, although there is little experience with such treatments (Becktor et al., 2002). The treatment of dental malocclusion in a progressively disfiguring condition can be challenging.

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This chapter is dedicated to the memory of Alex Hoag, Kyle Dullenkopf, and Sean Easly, three individuals who participated in the National Institutes of Health study. I hope that the sorrow of their families can in some small way be mitigated by the knowledge that their child's participation in the study has directly and significantly benefited current and future affected individuals with this disorder. I am indebted to them and to all of the other individuals and families who have participated. Early drafts of this chapter were reviewed by M. Michael Cohen, Jr., Thomas Darling, Douglas Schwartzentruber, Laura Tosi, and Joyce Turner. The author gratefully acknowledges their critical input, but the author is solely responsible for its content. The opinions expressed in this chapter are those of the author and are not to be construed as official recommendations by the Department of Health and Human Services, the National Institutes of Health, nor any other institution to which he is affiliated.

RESOURCES

Proteus Syndrome Foundation
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