Epidermal Nevus Syndromes

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The term "epidermal nevus syndrome" (ENS) has been used to describe the association of epidermal hamartomas and extra-cutaneous abnormalities. Epidermal nevi follow the lines of Blaschko. The majority of the extra-cutaneous manifestations involve the brain, eye, and skeletal systems. Several subsets with characteristic features have been delineated including the nevus sebaceous syndrome, Proteus syndrome, CHILD syndrome, Becker nevus syndrome, nevus comedonicus syndrome, and phakomatosis pigmentokeratotica. Epidermal nevi have been associated with benign and malignant neoplasms. Advances in molecular biology have revealed that the manifestations of ENS are due to genomic mosaicism. It is likely that the varied clinical manifestations of ENS are due in great part to the functional effects of specific genetic defects. Optimal management of the patient with ENS involves an interdisciplinary approach. Amelioration of the cutaneous features of ENS has been difficult but there have been advances, especially in the use of lasers.
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Solomon[1] proposed the term "epidermal nevus syndrome" (ENS) to describe the association of epidermal hamartomas and extra-cutaneous abnormalities. Although many continue to use the term "epidermal nevus syndrome," it is now understood that this is not one disease, but rather a heterogeneous group each with distinct genetic profiles but defined by a common cutaneous phenotype: the presence of epidermal and adnexal hamartomas that are associated with other organ system involvement. In the first comprehensive review of ENS, Solomon and Esterly[2] emphasized that although some hamartomas have more sebaceous differentiation (ie, nevus sebaceus [NS]), and others more epidermal differentiation (ie, keratinocytic epidermal nevi), many show differentiation toward several cutaneous appendages. This concept had been previously proposed by Mehregan and Pinkus[3] who described the clinical and histologic characteristics of NS from infancy to adulthood, building on Jadassohn's[4] original work. Jadassohn, in 1895, initially used the term "organnaevus" (organoid nevus) as a label in order to differentiate these hamartomas composed of keratinocytes and epidermal appendages from nevocellular (melanocytic) nevi.

The incidence of epidermal nevi (EN) has been reported to range from 1 to 3 per 1000 live births affecting males and females equally.[2,5] The percentage of individuals with EN who have extra-cutaneous abnormalities (ie, ENS) is not precisely known, and many estimates in the literature are overstated due to ascertainment bias. The largest and least biased series is that of Rogers,[6] who reported on 233 cases. The most common extra-cutaneous associations involve the central nervous system (CNS), ocular, and skeletal systems.

Diven has highlighted the importance of separating the extra-cutaneous manifestations associated with NS (ie, NS syndrome) from those associated with keratinocytic or "verrucous" epidermal nevi.[7] Happle[8] has expanded this idea and has proposed that several subsets of ENS should be differentiated from one another. These include the NS syndrome (also known as Schimmelpenning-Feuerstein-Mims syndrome), Proteus syndrome, CHILD syndrome, Becker's nevus associated with extra-cutaneous involvement (so called "pigmented hairy epidermal nevus" syndrome), nevus comedonicus syndrome, and phakomatosis pigmentokeratotica. Another prominent subset of ENS, keratinocytic ENS, could also be included in this list, although it is surely to be further subdivided in the future.

Advances in molecular biology have revealed that the manifestations of ENS are due to genomic mosaicism. Varied clinical manifestations of ENS may be due in large part to the functional effects of specific genetic defects and the timing of the mutation in fetal development. Unfortunately, since only a small minority of the genetic abnormalities causing EN have been discovered, complete biologic classification is impossible at the present time, and thus our descriptions and understanding continue to be primarily clinical. Once the genetic bases of different types of EN are more clearly delineated, the patterns of associated malformations are likely to be clarified more completely.[9]

This article discusses various facets of the ENS, including

Table 1 Associated Neurological Anomalies in Individuals With ENS[9]

Clinical	Structural
Seizures	Ventriculomegaly
Mental retardation/ developmental delays	Hemimegalencephaly
Hemi/quadriparesis	Cerebral vascular anomalies/infarction
Hypotonia/hypertonia	Cortical atrophy
Cranial nerve palsy	Posterior fossa abnormalities
Cortical blindness	Gyral abnormalities
Deafness	Hydrocephalus
Segmental dysesthesia	Calcifications
Macrocephaly/microcephaly	Lipoma
	Neoplasms
	Isolated enlargement of the temporal lobe
	Agenesis of the corpus callosum
	Porencephalic cyst

clinical presentations, histopathology, genetic basis, pathogenesis, and management.

Overview of Clinical Manifestations

The cutaneous features of EN depend in part on the predominant cell type involved, the degree of cellular differentiation, the body site of involvement, and the age of the patient. EN follow linear patterns known as "the lines of Blaschko." Blaschko's lines refer to the S-shaped or V-shaped whorled, streaked, and linear patterns that are recognized in many different cutaneous disorders. Blaschko meticulously recorded these lines[10] that do not follow any known nervous, vascular, or lymphatic structures in the skin.[11] Rather, they are felt by some to represent the dorso-ventral migratory pathways of the neuroectoderm during embryogenesis.[12]

The association of EN with CNS abnormalities has been recognized for many years. Schimmelpenning[13] and subsequently Feuerstein and Mims[14] were among the first to describe the association. Solomon and Esterly[2] provided the first comprehensive review of the associated neurologic (and other organ system) abnormalities. Since then, many reports and reviews have provided more detail and insight into the spectrum of the neurologic abnormalities associated with ENS (Table 1).[15-19] When other extra-cutaneous disease is also present, the incidence of CNS involvement becomes considerably higher, which may be a reflection of the inherent biologic severity of the causative mutation, or the timing of the mutation during development. Solomon and Esterly,[2] for example, found that 50% of patients with ENS have neurologic involvement. Estimates of the true incidence of CNS involvement in all patients with EN are probably as low as 5% to 15%, but have been hampered by ascertainment bias, the paucity of accompanying histological data on the EN, and inconsistency in obtaining imaging studies documenting the CNS abnormalities. In addition, definitions of clinical findings vary considerably in different reports. Finally, different epidermal nevus syndromes are likely to have distinct patterns of neurologic (as well as ocular and skeletal) involvement. Data on the incidence of extra-cutaneous features in some of the other subsets is sparse secondary to their relative rarity and the more recent characterization of some of these syndromes.

Nevus Sebaceus

Nevus sebaceus (NS) is relatively common, representing approximately one half of all EN.[6] NS is virtually always present at birth although some may not be noticed until later in childhood or until after puberty. Most have a salmon to yellow color and a characteristic smooth waxy surface (Fig 1). Mehregan and Pinkus[3] have described the natural history of NS, with an initial stage in infancy and childhood characterized by lesions that are relatively flat, due to the quiescence of sebaceous glands. At puberty, under hormonal influences, NS often thickens and develops papillomatous epidermal hyperplasia. Benign and malignant neoplasms characterize a third stage, which may be present in as many as 10% to 15% of cases. In Rogers'[6] series, nearly two thirds of NS were localized to the scalp and one-third to the face. Five percent were more extensive, involving scalp, face and neck, and in one case, the anterior chest.

By definition, NS syndrome involves a NS coupled with extra-cutaneous malformations usually involving the CNS, ocular, or skeletal systems. The major neurologic abnormalities include mental retardation and seizures. A review of 196 consecutive patients with NS referred mainly by their pediatricians and studied over a period of 16 years, revealed 7% with neurological manifestations.[20] The smaller incidence of associated neurological anomalies in this study compared with the many other sited reports likely reflects the inclusion of all EN in a prospective manner in a dermatology clinic. Extensive nevi were four times as likely in the patients with neurological manifestations compared to those without. Interestingly, a centro-facial location of the nevus was 10 times more likely in the patients with neurological abnormalities (21% compared to 2% of patients with NS in other locations). Mental retardation was found in 79% and seizures were present in 57% of neurologically affected patients. Neuroimaging was normal in the majority (75%) of those scanned

Fig 1 Nevus sebaceus on the face of a young child with nevus sebaceus syndrome.

with clinical neurological abnormalities. CNS involvement has been reported mainly in NS, but has been documented in association with keratinocytic EN, as well as in Proteus syndrome and in phacomatosis pigmentokeratotica (see below).

Both the site and type of epidermal nevus appear to influence the risk of CNS disease. In Grebe's review of 74 patients with ENS, skin lesions on the face and scalp correlated strongly with CNS involvement, while lesions limited to the trunk and limbs were less associated with CNS involvement.[2,15,21] The NS subtype is more prevalent on the head and neck, likely reflecting the regional predominance of sebaceous glands in this area. CNS disease has been reported in a higher percentage of NS than keratinocytic nevi. It is not entirely clear whether the mutations causing NS predispose to more CNS involvement or if involvement of head and neck by EN *per se* (irrespective of subtype) predisposes to neurologic anomalies. Moreover, some authors have not found as striking a correlation between location and neurologic abnormalities. Rogers found that the head was involved in only 3 of 7 patients with seizures, and in 7 of 18 with any form of neurologic abnormality.[19]

Ocular choristomas and colobomas are the most common ocular findings associated with NS syndrome. Although many reports that discuss the association of ocular anomalies in ENS do not distinguish between the subtypes of epidermal nevus, it appears that NS may be the most commonly associated. The series of Rogers,[19] found that 9% of 119 patients with EN had ocular anomalies, with strabismus being most common (6.7%). Grebe[15] reviewed 74 cases of ENS, selected because of the association with other multiple organ system abnormalities, and found ocular involvement in 39%. Lipodermoids were the most common (20%), followed by colobomas (9%), corneal opacities (7%), exo/esotropia (7%), retinal changes (scarring, degeneration, detachment, 7%), ptosis (5%), macroophthalmia (4%), and conjunctival growth disorders (3%).

Solomon and Esterly (1975) attempted to classify the skeletal abnormalities by separating them into primary osseous changes, and secondary changes, which may be attributed to another coexisting abnormality. Examples of primary skeletal abnormalities included incomplete formation of bony structures including ankle, foot, phalanges, and vertebrae, hypoplasia of pelvic bones and long bones, and bone cysts. Examples of secondary osseous changes included limb hypertrophy, kyphoscoliosis, asymmetry of the skull, short stature, spontaneous fractures and rickets. Rogers[19] found that 15% of 119 patients with EN had abnormalities of the skeletal system. However, many of the associated anomalies were minor and common in the general population and may have been coincidental. Grebe[15] reviewed the clinical features of 74 cases of ENS and found skeletal anomalies in 50%. The high incidence of skeletal abnormalities in their series reflects the inclusion of patients with other organ system involvement. They found a diverse range of abnormalities, many of which could be attributed to tissue overgrowth.

The histopathological features of NS change with age, as do the clinical features. Before puberty, the sebaceous glands are fairly small, but even at this stage, the presence of incompletely differentiated hair structures may suggest the diagnosis. Papillomatous epidermal hyperplasia, while more pronounced in older patients, is often present in young children. After puberty, one can find large numbers of mature sebaceous glands in addition to papillomatous hyperplasia of the overlying epidermis (Fig 2). Ectopic apocrine glands are identifiable in the majority of patients. The hair structures remain small except for occasional dilated infundibula. There are often buds of follicular germ that resemble foci of basal cell carcinoma, but usually represent follicular induction of primitive hair germ as discussed below.[22]

Keratinocytic EN

Keratinocytic EN are the other most common form of EN.[6] They appear as linear or whorled skin-colored to pink or slightly hyperpigmented plaques (Fig 3). They are usually present at the time of birth but many have their onset during early infancy, sometimes extending over adjacent areas of skin for the first few months to years of life. Initially they may be flat, but over time they often become more elevated, verrucous and darker in color. Acral lesions often have a more warty appearance.[2] When the nail matrix is affected, the nail may be dystrophic. In the body folds, lesions are softer and less verrucous. The distribution and extent of the EN varies widely: they can be solitary, multiple, large or small, and are commonly found on the trunk or extremities. Lesions may be either unilateral (so-called "nevus unius lateris"), or bilateral, usually stopping abruptly at the dorsal and ventral midline. When they are symmetric and bilateral they have been referred to as systematized EN or ichthyosis histrix. Keratinocytic EN are less common on the head and neck.[2,23]

Gurecki et al[24] reviewed 23 cases of biopsy proven EN with accompanying neurologic abnormalities. The authors also analyzed the results of CNS imaging studies including computerized tomography (CT). Cases of keratinocytic nevi and NS were approximately equal in numbers. Nevi were located on the head and/or neck in 91% of the patients and 55% of the patients had seizures. All cases of neonatal seizures and infantile spasms had major hemispheric malformations; 53% had mental retardation or developmental delays. Of these cases, most were considered moderately or severely impaired. The most common CNS structural abnormalities were hemiatrophy (26%), vascular anomalies (26%), cranial bone deformities (26%) hemimegalencephaly (22%), gyral abnormalities (22%), and posterior fossa abnormalities (9%).

In Rogers' study,[6] of the 106 cases of EN with a predominantly keratinocytic morphology, 18% had skeletal abnormalities although less than half of these (7%) were thought to have a strong likelihood of association. Mental retardation was present in 7%, seizures in 5% and strabismus in 5%.

"Keratinocytic epidermal nevus syndrome" has been left out of the characterization of defined subsets of ENS. Clearly, keratinocytic EN are associated with extra-cutaneous manifestations and the cutaneous features of keratinocytic EN are distinct from those of other ENS such as NS. The extra-cutaneous manifestations may be distinct as well, but this remains to be seen. However, this "subset" may not represent
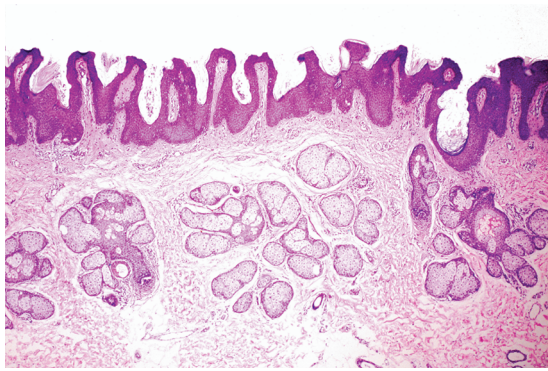
Fig 2 Hematoxylin and eosin stained section of nevus sebaceus showing papillated epidermal hyperplasia and subjacent abnormal folliculo-sebaceous glands.

a true syndrome because it surely encompasses several unique syndromes and thus will surely be subdivided in the future as specific molecular defects are identified and as specific clinical features are better characterized.

Histologically, keratinocytic, or verrucous EN are characterized by acanthosis, orthohyperkeratosis, papillomatosis, and an expanded papillary dermis which is sharply demarcated from the surrounding normal skin. One hundred sixty-seven biopsy specimens were analyzed from 160 patients with EN, excluding NS. The most frequent type showed hyperkeratosis and epidermal hyperplasia (67%), followed by acrokeratosis verruciformis-like features with marked hyperkeratosis, hypergranulosis, and acanthosis (13%), epidermolytic hyperkeratosis (5%), seborrheic keratosis-like features (5%), psoriasiform hyperplasia (3.6%), verruca-like features (2%), and 1.2% each of porokeratosis-like features, Darier's-like changes, and acanthosis nigricans-like features.[25]

Nevus Comedonicus

Nevus comedonicus is characterized by a localized collection of dilated follicles containing keratin. They have been found on the face as well as the trunk and upper extremity.[26] Scattered hair shafts and small sebaceous glands may be seen. Some cases have revealed epidermolytic hyperkeratosis histologically. Nevus comedonicus may be complicated by superinfection with bacteria, chronic inflammation and scarring.[27] Follicular tumors including trichofolliculoma and pilar sheath acanthoma have been documented within a nevus comedonicus.[28] Although reported neurological, ocular and skeletal anomalies have primarily been associated with NS, they are known to occur in association with other forms of EN and their patterns of association may be distinct. Electroencephalographic (EEG) abnormalities, ipsilateral cataract, corneal changes, and skeletal anomalies such as hemivertebrae, scoliosis and absence of the fifth ray of a hand have been associated with nevus comedonicus.[8,29,30] These extra-cutaneous associations have lead Happle and others to purport that nevus comedonicus syndrome is a distinct entity.

Child Syndrome

The acronym CHILD (Congenital Hemidysplasia with Ichthyosiform Nevus and Limb Defects) syndrome was introduced by Happle et al.[31] Earlier reports describing this entity had been published under the name "congenital unilateral ichthyosiform erythroderma."[32,33] The syndrome is seen almost exclusively in females and is believed to be transmitted as an X–linked dominant trait.[31] The cutaneous findings characterizing the syndrome are unilateral inflammatory erythematous patches often covered in dry yellowish scales. They often occur in body folds such as the vulva, axilla and the gluteal fold (so called "ptychotropism"), helping to distinguish CHILD syndrome from ILVEN. The nevus characteristically involves one side of the body with striking midline demarcation.[34,35] There may be thin bands of sparing following the lines of Blaschko. Interestingly, the cutaneous features of CHILD syndrome appear to undergo spontaneous partial regression during childhood. Histologically, the lesion shows psoriasiform epidermal hyperplasia with marked hyperkeratosis and parakeratosis, with sparse perivascular lymphocytic infiltrates. The extra-cutaneous features include ipsilateral hypoplasia of the limbs. These can vary from minimal hypoplasia of the phalanges to complete absence of an extremity. The skeletal changes are not necessarily limited to the limbs and have included the axial skeleton. Reported neurological anomalies include ipsilateral hemispheric hypoplasia and EEG abnormalities. Life threatening cardiovascular defects have also been reported.[31]

Becker Nevus (Pigmented Hairy Epidermal Nevus)

Becker nevus is characterized by a circumscribed patch of hyperpigmentation with hypertrichosis and slight acantho-

Fig 3 Keratinocytic epidermal nevus on the neck.

sis. When stroked or rubbed, Becker nevi become more elevated and appear more infiltrated (pseudo-Darier's sign) secondary to piloerection of the hairs within the nevus. This stems from the increased numbers of smooth muscle fibers of the erector pili contained within Becker nevi. The overlapping clinical features (hyperpigmentation, hypertrichosis, and increased smooth muscle bundles) between smooth muscle hamartoma and Becker nevus have prompted some to consider smooth muscle hamartoma and Becker nevus on a continuum.[36] Several differences, however, may indicate that these are distinct entities. Smooth muscle hamartoma is congenital whereas Becker nevus has its onset later in childhood and in adolescence. The Becker nevus is androgen dependent, becoming more prominent and developing coarse hair after puberty in males. Becker nevus is usually located in the shoulder region but up to 12% of cases have been noted on the lower extremity. Pruritus, lichen planus, and acneiform eruptions with comedones, papules, pustules, and cysts have been reported in association with Becker's nevi.[37] Becker nevi have been associated with ipsilateral hypoplasia of the breast, hypoplasia of underlying musculature, lipoatrophy, and underlying skeletal anomalies, including scoliosis, hemivertebrae, fused or accessory cervical ribs, pectus excavatum or carinatum, and internal tibial torsion.[38]

Proteus Syndrome

Proteus syndrome was first described by Cohen.[39] The clinical features of Proteus syndrome are highly variable and are characterized by overgrowth of multiple tissues. Typical findings include hemihypertrophy, asymmetrical macrodactyly, skull and other skeletal anomalies, epidermal and connective tissue nevi, lipomas, and vascular malformations. These features may be present at birth or develop over time. Cerebral involvement is not typical in Proteus syndrome but mental retardation with seizures and brain malformations have been reported. In 1998, a consensus conference was held to establish diagnostic criteria in order to better define and characterize the myriad of features associated with this syndrome. The general diagnostic criteria include mosaic distribution of lesions, progressive course, and sporadic occurrence. In addition, patients must have either a connective tissue nevus, or 2 of the following: epidermal nevus, disproportionate overgrowth, ovarian or parotid tumors, or 3 of the following: lipomas or fat hypo/aplasia, vascular malformations, characteristic facies.[40]

Phacomatosis Pigmentokeratotica

Phacomatosis pigmentokeratotica is defined by the association of speckled-lentiginous nevus and EN. Neurologic, ocular, and skeletal anomalies are variably present. Hemiatrophy with muscular weakness appears to be a common finding. Interestingly, while the EN follows the lines of Blaschko, the melanocytic component usually occurs in a checkerboard (broad segmental areas respecting the midline) pattern.[41] The neurological defects reported in association with PPK are segmental dysethesia, mild mental retardation, seizures, and deafness, ptosis, and strabismus.[41] In addition, PPK has been associated with bony asymmetry including hypoplasia of the pelvis, kyphoscoliosis, and hemi-atrophy.[42]

Inflammatory Linear Verrucous Epidermal Nevus

ILVEN (inflammatory linear verrucous epidermal nevus), described in 1971,[43,44] represents approximately 6% of all EN.[19] It is characterized by linear pruritic, erythematous, and hyperkeratotic papules that often coalesce into plaques (Fig 4). It is usually unilateral and often affects the lower half of the body with the buttock being the most frequently affected site.[19] It is often present at birth or develops with the first 6 months of life, which together with its resistance to standard treatment, and severe pruritus, may help to distinguish it clinically from psoriasis. A skin biopsy may be necessary to distinguish ILVEN from psoriasis. Histologically, ILVEN demonstrates ortho-hyperkeratosis alternating with parakeratotic hyperkeratosis.[45] Absent involucrin expression has been reported and also may be helpful in differentiating ILVEN from psoriasis.[46] There have been multiple reports of ILVEN associated with ipsilateral skeletal anomalies,[47] although others have called into question the association of ILVEN with extra-cutaneous manifestations. Lee and Rogers reviewed 23 cases over a 13 year period and found 2 with skeletal anomalies but in both cases they were bilateral and thought to be coincidental. It has been suggested that the original reports associating ILVEN with severe skeletal defects were in fact incorrectly diagnosed cases of CHILD syndrome.[48]

Porokeratotic Eccrine Nevus

Porokeratotic eccrine nevus (PEN) was originally described as "comedo nevus of the palm" by Marsden[49] and subsequently termed porokeratotic eccrine ostial and dermal duct nevus.[50] Happle prefers the term PEN as it is simpler and contains the relevant information regarding the pathology. Since the original description, there have been at least 25 reported cases of PEN. PEN consists of verrucous, keratotic papules with keratin filled invaginations representing eccrine ducts located on the palms and soles. The majority of cases present at birth or soon after. There have been 3 reports of widespread cutaneous involvement.[51,52]

Endocrine Abnormalities Associated with ENS

Sugarman and Reed[53] were the first to report the association of ENS with hypophosphatemic rickets. Since then, there have been at least 18 cases of hypophosphatemic vitamin D-resistant rickets associated with NS syndrome.[54] CNS abnormalities were present in 36% of these 14 cases and 12 out of 14 (86%) of these children had mental retardation. Rick-

ets, muscle weakness and bone pain developed at an early age in many of the patients. There has also been a case of phacomatosis pigmentokeratotica associated with hypophosphatemic vitamin D-resistant rickets.[55]

Yu[56] reported a case of ENS associated with the syndrome of inappropriate anti-diuretic hormone (SIADH). Their case involved an infant with seizures, hyponatremia and SIADH. There have been several reported cases of central precocious puberty associated with ENS.[57]

EN and Neoplasms

Several cutaneous malignancies including basal call carcinoma, squamous cell carcinoma, and adnexal carcinomas have been described in association with EN. Malignant transformation of EN may occur whether or not they are associated with other organ system abnormalities.[2,3] Until recently, NS was thought to have a 10% to 15% risk of malignant transformation, most commonly to basal cell carcinoma. Mehregan and Pinkus[3] analyzed 150 cases of EN and found 52 tumors in 33 patients. These included basal cell carcinoma,[21] syringocystadenoma papilliferum,[8] syringoma, apocrine cystadenoma, apocrine carcinoma, hidradenoma, and sebaceous epithelioma.

Subsequent reports however have modified our understanding of the biologic behavior of NS. Domingo[58] described 9 cases of aggressive malignant neoplasms associated with NS and reviewed the literature. In their study, malignant transformation occurred in older adults (median age 64.5 years) and was associated with aggressive neoplasms including squamous cell carcinoma, apocrine carcinoma and other adnexal carcinoma. Rogers[19] found secondary tumors in only 7% of EN, including invasive squamous cell carcinoma, and a keratoacanthoma-like lesion.

More recently, the magnitude of the malignant potential of NS has been questioned. Cribier[59] retrospectively analyzed 596 cases of NS, 79% of which were located on the scalp. They found benign tumors in 14% of these, the most common of which included syringocystadenoma papilliferum (5%), trichoblastoma (5%), trichilemmoma (3%), and sebaceoma (2%), but found basal cell carcinoma in only 0.8% of cases. Interestingly, many of the cases of trichoblastoma (a benign neoplasm) had originally been classified as basal cell carcinoma but were re-diagnosed using new criteria. Similarly, a retrospective analysis of 155 cases of NS by Jaqueti[60] found neoplasms in 21% with trichoblastoma being most common (7.5%), followed by syringocystadenoma papilliferum (6%), and sebomatricoma (5%). Smaller numbers of apocrine hidrocystoma and apocrine poroma were also found. There were no cases of malignant neoplasm found. The decreasing incidence of tumors developing in NS could be the result of more frequent early excision for cosmetic reasons, but the data from Jaqueti suggest otherwise; 61% of their cases were from adults. It seems likely that most of the tumors arising in NS that have in the past been interpreted as BCC are in fact examples of primitive follicular induction or trichoblastomas, and not authentic BCC.

While there is much analysis in the literature of the his-

Fig 4 Inflammatory linear epidermal nevus (ILVEN), following the lines of Blaschko.

topathological features of cutaneous lesions in ENS, pathologic descriptions of CNS findings in such patients are rare. Prayson[61] examined the clinicopathologic features of 3 patients with ENS who underwent surgical resections for chronic epilepsy. Microscopic examination of resected cortical tissue demonstrated severe diffuse cortical dysplasia characterized by a disorganized cortical architectural pattern, a haphazard orientation of cortical neurons, and increased molecular layer neurons. There was also prominent cortical astrocytosis. Gyral fusion was seen in 1 patient. Pial glioneuronal hamartomas were observed in 1 patient. Neuronal heterotopia was observed in all 3 patients. Similarly, Pavone[62] noted a disturbed laminar pattern of the cerebral cortex on microscopic analysis of a patient with neurological involvement. In addition, they noted atypical giant neurons, heterotopic neurons in both the white matter and the subarachnoid space, areas of marked astrocyte proliferation infiltrating into adjacent structures and small angioma-like conglomerations of blood vessels. From an architectural standpoint, this is analogous to the hamartomatous structures observed microscopically in EN.

Genetic Basis and Pathogenesis

Many lines of evidence suggest that the pathogenesis and clinical expression of ENS is based on genomic mosaicism. Mosaicism is the mixture of more than one genotypically distinct cell lineage within one organism. Epidermal cells are thought to originate in the neural crest and move to the periphery of the growing embryo by directional proliferation.[12] A somatic mutation occurring during the migration of embryonic ectoderm will only be clinically apparent if the mutation leads to a recognizable difference from the surrounding normal cells, which follow Blaschko's lines. Thus, Blaschko's lines are believed to be a cutaneous expression of mosaicism. In this conceptual framework, mutations which occur earlier in development would lead to more extensive cutaneous involvement and a greater likelihood of other organ system involvement. In addition, the biologic severity of a particular mutation is also likely to determine the extent and severity of clinical involvement.

The concept of lethal genes surviving by mosaicism has

been proposed by Happle[63] to explain the sporadic inheritance, asymmetric clinical distribution in multiple organs, the lack of diffuse involvement of entire organs, and the equal sex ratio of affected individuals that characterize the features of ENS. Happle postulated that these syndromes are due to the action of a gene product that if present in the germ line would be lethal, but is clinically manifested only when present in a subpopulation of cells, thereby surviving by mosaicism. However, mosaicism in ENS may involve a nonlethal gene defect as is the case with epidermolytic hyperkeratosis. In the mosaic form, there is an EN of the epidermolytic type. If the gene defect is also present in the germ cells, this nonlethal mutation may be transmitted to the next generation as generalized bullous congenital ichythyosiform erythroderma (epidermolytic hyperkeratosis).[63]

Several specific examples have provided evidence that genetic mosaicism can cause the cutaneous phenotype of EN (Table 2). Zamora[64] reported a case of a woman with a widespread verrucous epidermal nevus and multiple trichilemmal cysts in whom they discovered chromosomal mosaicism in which 5% of her lymphocytes contained a translocation between 1p36 and 9q34. Stosiek[65] performed cytogenetic analysis on keratinocytes from 2 patients with EN and found a translocation at the same breaking point in chromosome 1. Paller[18] found point mutations in 50% of the keratin 10 alleles of epidermal cells from patients with EN (of the epidermolytic type) while finding no mutations in adjacent clinically normal skin. They also found the same mutations in 50% of the keratin 10 alleles in all the cell types examined from their offspring. Similarly, Moss[66] has provided evidence of a keratin 10 mutation in affected cells of an individual with linear EN while showing that cells from unaffected adjacent epidermis had no mutation. Keratin 1 gene mosaicism has also been identified in an epidermal nevus (of the epidermolytic type) in a woman whose son has epidermolytic hyperkeratosis and the identical genomic mutation. This is not surprising, as keratins 1 and 10 are obligate partners providing function to the epidermis in a cell type-specific manner. There is one report of chromosomal mosiacism associated with Becker nevus syndrome, although the specific cytogenetic abnormalities could not be identified.[67]

Munro and Wilkie[68] reported on a 14-year-old boy with a nevus comedonicus who had a mutation in the fibroblast growth factor receptor 2 (FGFR2) identical to that found in Apert's syndrome. The mutation was found in DNA analysis from the nevus comedonicus, but not from uninvolved skin or peripheral blood lymphocytes. This suggests that nevus comedonicus represents a mosaic condition for a mutation in FGFR2, which if present in the germ line, would result in Apert's syndrome. It also provides a framework for understanding the association of nevus comedonicus with skeletal anomalies. Apert's syndrome is characterized by skeletal anomalies such as craniosynostosis, syndactyly, fusion of cervical vertebrae and acne. Individuals with nevus comedonicus and skeletal anomalies (ie, nevus comedonicus syndrome) may be mosaic for FGFR2 in both skin and extra-cutaneous tissues secondary to a mutational event occurring

earlier in development than seen in individuals without extra-cutaneous involvement.

The molecular basis of CHILD syndrome has recently been elucidated. CHILD syndrome is caused by a mutation in the NSDHL gene encoding a 3β-hydroxysteroid dehydrogenase. This protein functions in cholesterol biosynthetic pathway.[69] Previous reports had revealed decreased numbers of peroxisomes and reduced activity of peroxisomal enzymes in involved skin fibroblasts in patients with CHILD syndrome.[70] Peroxisomes contain enzymes catalyzing a number of indispensable metabolic functions mainly related to cholesterol metabolism.[71] A defective response to Hedgehog signaling is now thought to play a role in disorders of cholesterol biosynthesis[72] that share some of the skeletal and cardiovascular defects seen in CHILD syndrome.

In one report, loss of heterozygosity of the patched gene, which is known to be involved in the development of basal cell carcinoma, was found in 40% of the NS that were analyzed. It is unclear whether patched deletion in NS is associated with the propensity to develop basal cell carcinoma or other benign appendageal tumors.[73]

Mutations in the tumor suppressor gene PTEN have been associated with several hamartomatous tumor syndromes and overgrowth syndromes including a Proteus-like syndrome in an individual with an epidermal nevus.[74] As the genetic basis for these overgrowth syndromes becomes more clearly understood, the associations linking these seemingly disparate clinical phenotypes may be better clarified.

The rare hypophosphatemic vitamin D-resistant rickets that is associated with NS is thought to result from abnormal phosphate excretion secondary to defective renal tubular reabsorption of phosphate. Some authors have proposed that this condition is analogous to the rare association of hypophosphatemic vitamin D-resistant rickets associated with mesenchyme-derived neoplasms (tumor-induced osteomalacia), in which the tumor produces a phosphaturic factor that leads to osteomalacia.[75,76] Recently, the phosphaturic factor responsible for tumor-induced osteomalacia has been identified. These tumors secrete large amounts of FGF23.[77] Similarly, patients with autosomal dominant hypophosphatemic rickets have increased levels of circulating FGF23 due to the production of a mutant FGF 23 that makes it resistant to cleavage and degradation.

There have been reports of at least partial reversal of the hypophosphatemia with removal of a portion of an epidermal nevus.[55,75,78] In one compelling case report, a 12-year-old patient with large facial EN and vitamin D-resistant hypophosphatemic rickets improved following excision of several fibro-angiomatous EN. Serum phosphate concentrations and tubular reabsorption of phosphorus both increased significantly after excision. These authors then homogenized the EN that had been initially removed, and infused them into the femoral vein of a dog. Two hours after the infusion, the tubular reabsorption of phosphorus decreased dramatically. Control infusions had no effect on phosphorus reabsorption. Based on these findings, they speculated that EN produce a phosphaturic factor that leads to osteomalacia.[75] It appears likely that the hypophosphatemic rickets seen asso-

ciated with NS is due to either overproduction of FGF23 (wild type or mutant) or involves another molecule regulating the phosphate homeostasis and skeletal mineralization axis.

The cortical dysplasia seen in individuals with ENS likely represents derangement in neuronal migration, much of which occurs in the first two trimesters of gestation. It is well recognized that cortical dysplasia is associated with epilepsy and may be at least partly responsible for the increased incidence of seizures in ENS. In addition, cortical dysplasia has also been associated with certain low-grade neoplasms including ganglioneuromas, implicating a common underlying etiology for the abnormal neuronal migration in patients with ENS and the development of these tumors.[61,79] It appears that at least in a subset of patients with neurological involvement, primary vascular anomalies may lead to secondary CNS pathology. For example, infarcts, atrophy, porencephaly, and calcifications are best explained in some cases by prior ischemia or hemorrhage.[62]

It is well documented that FGFs play a vital role in embryonic development. They function as important signaling molecules between epithelial and mesenchymal boundaries.[80] Mutations in FGFs have been associated with developmental defects in neuronal, skeletal, and ocular, and cardiovascular systems. Because the product of a single gene may be involved in the formation of different structures at distinct times during embryogenesis, a single genetic defect may cause anomalies of multiple structures in different organs during development. In addition, different genetic defects may give rise to similar phenotypes by disruption of embryogenesis at a common point in time. Despite the characterization of distinct epidermal nevus syndromes, classification of the majority of the developmental defects seen in ENS has not yet occurred. Investigation of the role of FGF mutations in ENS may provide insight into the pathogenesis of the cutaneous and extra-cutaneous features of these syndromes. The analysis of mutations from different EN will undoubtedly clarify the range of genetic defects and enhance our understanding of the role of genetic aberrations in the pathogenesis of the cutaneous and extra-cutaneous features seen in these disorders.

Management Issues

The management of the patient with ENS needs to be individualized, and should always include a thorough history including prenatal history, developmental history, and family history. Careful and complete cutaneous examination should include the mucosa and areas covered by hair. A careful neurological exam is critical, as is examination of the eyes, especially the conjunctiva, sclerae, and extra-ocular eye movements. Skeletal exam should include evaluation for kyphoscoliosis and evaluation of gait. Limb length and size should be measured to ascertain any asymmetry. Shoe wear patterns can serve as a clue to uneven weight distribution. Referral to appropriate subspecialists should be considered.

Generally, children with small isolated EN and a normal physical exam do not require further work-up (except per-

Table 2 Genes Identified in Selected Epidermal Nevi

Disorder	Associated Mutation
NS	Patched
Epidermolytic EN	Keratins 1 and 10
CHILD syndrome	3β-hydroxysteroid dehydrogenase
Nevus comedonicus	Fibroblast growth factor receptor 2
NS associated with rickets	Fibroblast growth factor receptor 23 (not confirmed)
Proteus like syndromes	PTEN

haps skin biopsy, see below). Diagnostic and screening laboratory investigations should be performed if abnormalities are suspected after history and physical exam. The choice of imaging studies should be individualized depending on the nature of the suspected abnormalities and might include skull and chest radiographs, skeletal survey, CT scan of the head, MRI, and EEG. Any child with an epidermal nevus on the head or neck and developmental delay should be imaged even though the yield may be low. Seizures tend to occur early, if they are going to be manifested, and follow-up until school age is probably adequate for those in whom there are no neurological abnormalities. Laboratories such as electrolytes including serum and urine calcium and phosphate, and liver and renal function tests should be considered when appropriate. An interdisciplinary approach may need to be adopted depending on the type and extent of other organ involvement and may require the coordination of different specialists including a dermatologist, pediatric neurologist, ophthalmologist, orthopedic surgeon, oral surgeon, plastic surgeon, and psychologist.

Skin biopsy may be of benefit in some cases. It is certainly indicated to evaluate the possibility of malignancy if a particular area of an EN is changing, especially in NS, where there is a small but significant risk of the development of cutaneous malignancy. In the case of keratinocytic EN, the microscopic findings of clumping of keratohyaline granules suggest a mutation in keratins 1 or 10. The sensitivity of skin biopsy for detecting these findings is not known, and their absence does not exclude the possibility of keratin mutations.

Referral to a medical geneticist may be warranted for further evaluation including gene testing regarding the possibility of transmission of a more generalized form of this disease (epidermolytic hyperkeratosis) or Apert's syndrome (in the case of nevus comedonicus) to future offspring. The role of genetic counseling in other lesions is uncertain.

Prophylactic excision to prevent possible future malignancy may not be appropriate especially if the surgery itself will be disfiguring. For NS, this approach was undertaken more often in the past when it was thought that the malignant potential was much greater than it is now known to be today. A more practical approach may be to intervene with an incisional biopsy for any new growth in the nevus to precisely determine its nature. Excision of EN may also be warranted to ameliorate the disfigurement caused by the nevus itself. However, simple excision may not always be practical because of the location or size of the EN. In addition, because abnormalities in EN frequently involve not only the epidermis but also appendageal structures in the underlying der-

mis, removal of the epidermis alone may result in recurrence.[2,18] Many alternative treatments of EN have been reported. Unfortunately, the efficacy of these alternative therapies is uncertain due to the lack of controlled trials. Many of the following therapeutic interventions are based on individual case reports where long-term follow-up is lacking. There have been reports of the successful use of carbon dioxide (CO2) laser to remove linear EN without any obvious scarring,[81,82] but in many cases visible scars are evident, particularly if continuous wave CO2 laser is used. The Q-switched ruby laser is occasionally effective in treating pigmented EN including Becker's nevus.[83] Topical vitamin D3 (calcipotriol 0.005%) has been tried in the treatment of ILVEN where its most prominent effect was to relieve associated pruritus. Calcipotriol decreased the erythema and hyperkeratosis but the effects were only permanent in one patient.[84,85] However, others have reported that calcipotriol is ineffective in treating the cutaneous features or the associated pruritus in ILVEN.[48] A large linear epidermal nevus was successfully treated with a combination of topical tretinoin and 5% 5-fluorouracil (Efudex) with marked improvement. Unfortunately, the nevi recurred after 3 to 4 weeks, but the authors reported that reinitiation of therapy 2 to 3 times a month has had excellent results.[86] There is one report of shave excision using a dermatome followed by phenol peeling for the treatment of a verrucous epidermal nevus with a reportedly good outcome.[87] Other approaches reported in the treatment of EN have included cryotherapy, keratolytics, and intralesional steroids, but none have been substantiated in controlled studies. Long-term follow-up is lacking from many of these case reports. As our understanding of the pathogenesis of EN expands, future management may be directed toward specific molecular defects.

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