Epidermal nevus syndrome

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Creation date: April 2004

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Abstract
Epidermal nevus syndrome (ENS) is a rare congenitally acquired syndrome, characterized by the presence of epidermal nevi in association with various developmental abnormalities of the skin, eyes, nervous, skeletal, cardiovascular and urogenital systems. Epidermal nevi are developmental disorders characterized by hyperplasia of epidermal structures in a circumscribed area of the skin. Most are present at birth, occur sporadically and affect both sexes. All well-defined ENS are lethal gene syndromes, except nevus comedonicus syndrome. About 50% of the patients have neurological abnormalities that include mental retardation and epilepsy, spastic paresis, cerebral vascular malformations, cortical atrophy, lateral ventricle enlargement. About one third of the patients may have ocular abnormalities such as colobomas of the eyelid, iris and retina, conjunctival lipoderoids and choristomas, cortical blindness, micro-, macro- or anophthalmia, corneal opacities and cataracts. Skeletal abnormalities and many other non-cutaneous abnormalities may be present. No ideal medical therapy for the cutaneous lesions of ENS exists. The skin lesions may be amenable to surgery. The inflammatory linear verrucous epidermal nevus (ILVEN) sometimes responds to Erbium-YAG laser or vitamin D analogues. Salicylic acid, topical and systemic retinoids, emollients, shave dermabrasion and cryotherapy have been tried. The concomitant skeletal and ocular defects can be surgically repaired. Epilepsy should be treated appropriately.

Keywords
Solomon syndrome, nevus comedonicus, Proteus syndrome, CHILD syndrome, Schimmelpenning-Feuerstein-Mims syndrome, Becker nevus syndrome, Phacomatosis pigmentokeratotica syndrome, nevus unius lateris, ILVEN

Definition
Epidermal nevus syndrome (ENS), often termed the Solomon syndrome, is a congenitally acquired syndrome, characterized by the presence of epidermal nevi in association with various developmental abnormalities of the skin, eyes, nervous, skeletal, cardiovascular and urogenital systems (1). Epidermal nevi are developmental disorders characterized by hyperplasia of epidermal structures in a circumscribed area of the skin. They occur sporadically and affect both sexes. Most are present at birth and frequently follow the lines of Blaschko (2). They can be divided into genuine epidermal nevi and organoid nevi, showing changes of adnexal structures (3).
Etiology and pathogenesis
In some instances the somatic mutation causing the syndrome must occur slightly early in embryonic life, so that mesenchymal and endodermal structures are also involved. While often the underlying changes are ipsilateral with the skin changes, they may be contralateral or even bilateral depending on the limiting of the mutation. It is not surprising that a wide variety of changes can be seen (4). All well-defined ENS are lethal gene syndromes, except nevus comedonicus syndrome, which represents mosaicism of Apert syndrome. The concept of autosomal lethal genes surviving only in a mosaic state was proposed by Happle to explain the genetic basis of several syndromes characterized by (almost always) sporadic occurrence, distribution of lesions in a scattered asymmetrical pattern, variable extent of involvement, lack of diffuse involvement of entire organs and equal sex ratio. The mosaic may either arise from a genetic half-chromatid mutation, or from an early postzygotic or somatic mutation during development. However, the gene defects resulting in those non-mendelian syndromes are mostly unknown (5).

Clinical description
A spectrum of epidermal nevi may be represented in this syndrome. Epidermal nevi seen, from most to the least common, include: nevus unius lateris, ichthyosis hystrix, acanthotic form of epidermal nevus, inflammatory linear verrucous epidermal nevus, nevus sebaceous, Becker nevus, nevus comedonicus, dermatitic epidermal nevus and nevus cystadenomatous papilliferus. Other mucocutaneous lesions include: lipomas, hemangiomas, striae keratoderma, pigmentary changes, hair and dental abnormalities, dermatomegaly (increase in skin thickness, warmth and hairiness), angiomatous nevi, nevi flammi, multiple hair follicle nevi, hypochromic nevi, café au lait macules and congenital melanocytic nevi (1,2,6,7). In a number of patients, the nevi involve the mucosae of the mouth, anus and genitalia. The oral involvement may include dental enamel hypoplasia, malformations of the teeth and hypodontia (6). Many neurological abnormalities have been identified in the ENS. They occur in 50% of patients. Though the general impression is that the neurological abnormalities are more frequent in patients whose epidermal nevi are on the head and the neck, it remains under question. Mental retardation and epilepsy are both common, being present in about 40% and 30% of the cases respectively. The fits might be focal or generalized, or infantile spasms. Mental retardation varies in degree but may be grave. Spastic hemiparesis affects about 20% of the patients and may have its onset at any time from birth to adolescence. Spastic tetraparesis has also been described. Cerebral angiomas and other vascular malformations are also common and many of the neurological abnormalities observed in these patients may have arisen as a result of pressure or haemorrhage from such lesions. Cortical atrophy, lateral ventricle enlargement, porencephaly, intracranial hamartoma, cranial nerve pulsies, hemimegalencephaly and encephalocele have also been described (2,6). Computerised tomography has revealed cerebral atrophy and focal densities resembling those seen in tuberous sclerosis.
About one third of the patients have ocular abnormalities, the commonest of which has been involvement of the eyelid or conjuctiva by the epidermal nevus, sometimes interfering with lid closure. Other ocular problems include colobomas of the eyelid, iris and retina, conjuctival lipodermoids and choristomas, cortical blindness, microphthalmia, macrophthalmia, anophthalmia, conal opacities and cataracts (6). Skeletal abnormalities include kyphoscoliosis, congenital dislocation of the hip, hypertelorism, limb reduction defects, syndactyly, polydactyly, lytic changes, bifid thumb, clinodactyly and short stature. Many other non-cutaneous abnormalities have now been reported in association with epidermal nevi, including bilateral sensorineural deafness, endocrine disease, ainhum-like digital constriction and autoamputation of the right fifth toe (8). There are a number of different features with only partially distinctive clinical features (4).

Proteus syndrome
It is a rare hamartomatous disorder (9). All cases have been sporadic. Proteus was a Greek god who was polymorphous and able to change his shape at will. Wiedemann chose this name for the syndrome to indicate the dramatical variability in its clinical appearance. The most striking cutaneous findings are hyperkeratotic epidermal nevi and palmoplantar connective tissue nevi that produce cerebriform changes of the hands and feet. A variety of mesenchyme...
malformations can also be seen, including nevus flammeus, hemangioma, lymphangiomas, nevocellular nevi, connective tissue nevi, café au lait-macules, macular hyper- or hypopigmentation (linear or whorled) and lipomas.

Concerning the systemic findings, it is reported an asymmetric growth which may result in macrocephaly, unequal limbs, enlarged of distorted hands and feet and a variety of other malformations like kyphosis, scoliosis, exostosis, skull abnormalities (enlarged or asymmetric), osteoporosis, digital hypertrophy and partial gigantism of hands and/or feet.

Ocular defects are common and highly variable (4). They include epibulbar tumors, strabismus, enlargement of the globe, cataracts and ptosis (10). Moderate mental retardation is present in about 50% of the patients. Despite the hamartomatous nature of the disorder, malignant degeneration appears rare (4). Other findings include seizures, testicular tumors and accelerated growth in the early life (10). Dermatological management has little to offer. Skilled orthopaedic care correct some of the skeletal defects. In other cases, amputation is the only answer.

**CHILD syndrome**

Almost all patients are women who in addition to the typical CHILD nevi have ipsilateral skeletal, CNS, pulmonary, cardiac and renal anomalies. Patients with ILVEN and systemic defects probably have CHILD syndrome.

**Schimmelpenning-Feuerstein-Mims syndrome**

Also known as nevus sebaceous syndrome, this disorder is characterised by one or more patches of nevus sebaceous associated with underlying central nervous system, ocular, cardiac and skeletal defects. Patients with more widespread nevii are probably at a greater risk of having underlying disease.

**Nevus comedonicus syndrome**

Rarely, patients with nevus comedonicus may also have ipsilateral, skeletal and ocular problems (4). One case of atrophoderma vermiculatum-like lesions associated with ipsilateral congenital cataract, ipsilateral alopecia and a seizure disorder has been reported. This might be an atypical form of nevus comedonicus syndrome (11).

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**Becker nevus syndrome**

This well known type of organoid nevus does never follow the lines of Blaschko but shows a checkerboard arrangement (3). The hallmark of Becker nevus syndrome is ipsilateral breast hypoplasia. For this reason, the syndrome is most often described in women, despite the fact that Becker nevi are more often identified in men, where the terminal hairs are more visible. In reality, both the isolated nevi and the syndrome are equally common in both sexes. Additional changes may include ipsilateral skeletal changes, usually hypoplastic in nature. Becker nevus syndrome might be found in families, the explanation being predominant inheritance.

**Phacomatosis pigmentokeratotica syndrome**

This syndrome appears as a combination of nevus sebaceous and nevus spilus with a variety of other problems. Associated findings may include hemiatrophy, cutaneous vascular malformations, segmental dysesthesias or hyperhidrosis and several types of CNS and ocular malformations. Loss of heterozygosity is the usual explanation for the almost mirror image pairing of two unrelated defects, presumably caused by genes which are close together in a given chromosome (4).

**Other**

Recently, two new types of ENS have been described: a) in a 20 years old-man with depigmented bilateral hypertrichosis and dilated follicular orifices following Blaschko’s lines associated with cerebral and ocular malformations, which is probably a neurocutaneous syndrome caused by mosaicism (5); and b) in a 16 years old boy. The latter case was characterized by systematized bands of non-epidermolytic hyperkeratosis with increased hairiness and follicular hyperkeratosis in addition to hemihypoplasia of limbs, branchy dactyly, clinodactyly and onychodystrophy (3).

**Epidemiology**

The syndromes are uncommon. Schimmelpenning-Feuerstein-Mims syndrome and nevus comedonicus syndrome have a female-to-male ratio of 1:1. ILVEN has a female predominance, with a female-to-male ratio of 4:1. Almost all patients with CHILD syndrome are women.

**Course and prognosis**

While significant developmental anomalies occur in approximately 1.7% of...
all neonates, a figure close to 10% probably applies in children with epidermal nevi. Since the risk of such abnormalities increases with increasingly widespread distribution of the skin lesions, serious non-cutaneous developmental defects may be found in children with a single epidermal nevus (6). Rarely, malignant transformation of epidermal nevi may occur. Transformation is most common with nevus sebaceous. The syndrome may also be associated with various visceral malignancies such as Wilm's tumor, astrocytoma, adenocarcinoma, ameloblastoma, ganglioneuroblastoma, oesophageal and stomach carcinoma, squamous cell carcinoma (1, 8), salivary gland carcinoma, transitional cell carcinoma of the bladder, rhabdomyosarcoma of the bladder and intrathoracic teratoma. In general, the prognosis depends on the presence and the severity of any of a variety of associated internal defects.

**Therapy**

No ideal medical therapy for the cutaneous lesions of ENS exists. The skin lesions may be amenable to surgery (4). The inflammatory linear verrucous epidermal nevus (ILVEN) sometimes responds to Erbium-YAG laser but there is a tendency for recurrence, unless much of the underlying dermis is destroyed along with the epidermal component. Also, salicylic acid, topical and systemic retinoids, shave dermabrasion and cryotherapy have been tried (12). Emollients such as hydrated petrolatum, vaseline, mineral oil have sometimes been used (1). The vitamin D analogue calcipotriol may be tried in each form of ENS, particularly ILVEN. The concomitant skeletal and ocular defects such as cataracts and lid anomalies can usually be surgically repaired. The CNS defects may lead to epilepsy which should be treated appropriately. Periodic electroencephalograms and skeletal radiological analysis may be important to the long-term care of the patient.

**Genetic counselling**

The patient and/or the family should be reassured that the ENS is not a genetic disorder that can be passed to future children.

**References**