

Encephalocraniocutaneous lipomatosis: A case report and review of the literature

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Encephalocraniocutaneous lipomatosis (ECCL) is a rare, sporadic congenital neurocutaneous disorder that characteristically involves ectomesodermal tissues, such as skin, eyes, and central nervous system. A 3-day-old girl presented with swelling in her right eye since birth. Ocular examination of the right eye showed hypertrophy of bulbar conjunctiva with limbal dermoid, clouding of cornea, and atypical upper eyelid coloboma. The left eye showed conjunctival congestion and corneal

vascularization. Dermatological examination showed alopecia, nevus psiloliparus, focal dermal hypoplasia on forehead, multiple focal aplastic lesions on the scalp, skin tag at canthus, and lipoma in the fronto-temporal region. Imaging revealed calcification of the right globe, hydrocephalus, agenesis of corpus callosum, multiple intracranial cysts, calcification, and lipomas. The constellation of these clinical and the imaging findings led to a diagnosis of encephalocraniocutaneous lipomatosis. This case report and review of the literature is presented to provide a synopsis of problems likely to be encountered by an ophthalmologist who treats patients with ECCL.

Key words: Haberland syndrome, oculocerebrocutaneous syndrome, encephalocraniocutaneous lipomatosis syndrome, neurocutaneous syndrome, Delleman-Oorthuys syndrome, Fishman syndrome

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Encephalocraniocutaneous lipomatosis (ECCL) formerly known as Haberland or Fishman syndrome is a rare, sporadic congenital neurocutaneous disorder that characteristically involves ectomesodermal tissues, such as skin, eyes, and central nervous system (CNS).^[1,2]

ECCL has classical triad of cutaneous abnormalities (nevus psiloliparus, subcutaneous lipoma in the fronto-temporal region, focal dermal hypoplasia or aplasia, small nodular tag on the eyelid or at outer canthal area), ocular abnormalities (choristomas, colobomas, corneal or anterior chamber abnormalities, and globe calcification), and CNS abnormalities (intracranial or intraspinal lipoma, abnormal intracranial vessels, complete or partial atrophy of a hemisphere, asymmetrically dilated ventricles or hydrocephalus, arachnoid cyst, porencephalic cyst, and calcification).^[1] Here, a unique and rare case of a 3-day-old girl with diagnosis of ECCL is being reported. This case report and review of literature is presented to provide a synopsis of the problems likely to be encountered by an ophthalmologist who treats patients with this syndrome.

Case Report

A 3-day-old Indian girl was referred to the oculoplasty clinic for

ophthalmic evaluation. She was admitted in pediatric intensive care unit for right-sided multifocal clonic seizures and was well controlled with phenobarbital. The baby was born out of non-consanguineous marriage, by normal vaginal delivery at term, to a primigravida mother with an uneventful pregnancy.

General physical examination at birth showed: Length 48 cm (50th centile), weight 2.5 kg (5th centile), and head circumference 38 cm (97th centile). Ophthalmic examination showed proptosis of the right eye, mechanical ptosis, upper eyelid atypical coloboma, ocular discharge, bulbar conjunctival hypertrophy, limbal dermoid of 4 × 3 mm extending from 1 to 5 O'clock, and corneal clouding [Figs. 1 and 2a]. The left eye showed conjunctival congestion, corneal vascularization extending from 12 to 2 O'clock, and rest of the anterior segment was normal [Fig. 2b]. Fundus examination of the right eye showed chorioretinal coloboma and optic disc coloboma. Fundus examination of the left eye was normal. Dermatological examination showed soft, nodular mass at right lateral canthus; measuring 7 × 7 mm, multiple patches of alopecia, 'nevus psiloliparus,' 'S'-shaped hypoplastic skin lesion extending from mid-forehead to root of the nose, multiple punched out lesions (focal skin aplastic

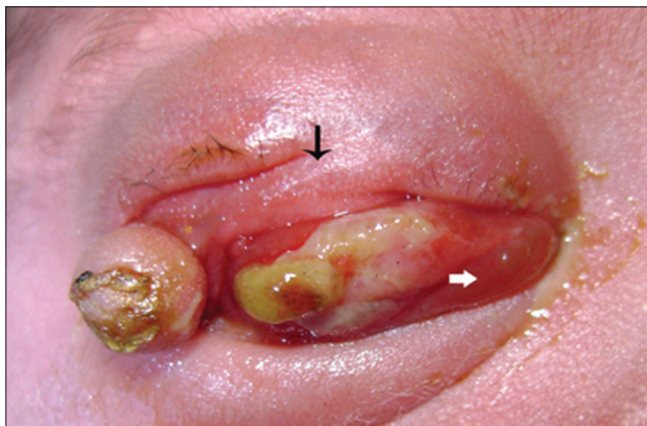


Figure 1: Mechanical ptosis and proptosis of the right eye, upper eyelid coloboma (black arrow), fullness in eyelids, conjunctival hypertrophy (white arrow), and conjunctival discharge

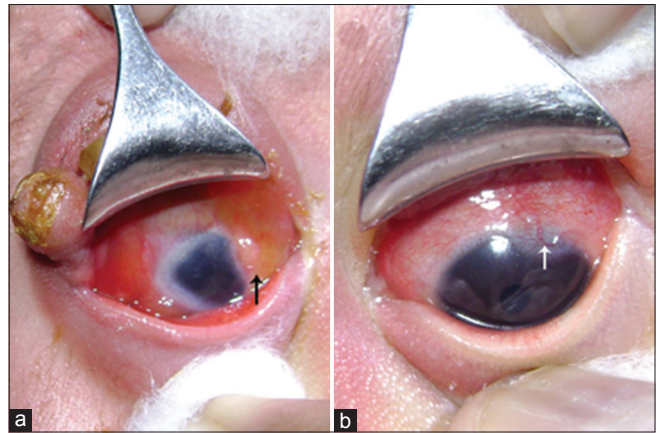


Figure 2: (a) Corneal clouding and vascularization, bulbar conjunctival hypertrophy, and nasal limbal dermoid (black arrow) in the right eye (b) Conjunctival congestion and corneal vascularization (white arrow) in the left eye



Figure 3: Hypoplastic skin lesion at forehead (black asterisk), lipoma in right fronto-temporal region, (white arrow) and large ipsilateral nevus psiloliparus (arrowhead) and skin tag at right lateral canthus (black arrow)



Figure 4: Large nevus psiloliparus extending from right side of the cheek to the fronto-temporo-parietal area of scalp (black arrows) and focal dermal aplasia in right temporal region of scalp (blue arrows)

lesions) on the occipital region of the scalp, and a lipoma in the fronto-temporal region [Figs. 3-5]. The child had multifocal clonic seizures mainly confined to right side of body. Neurological examination displayed hypotonia. Conjunctival swab from the right eye grew *Staphylococcus aureus* that was sensitive to ciprofloxacin, tobramycin, and oxacillin. Topical tobramycin 0.3% solution, four times a day was prescribed resulting in resolution of ophthalmia neonatorum. Incisional biopsy was taken from hypertrophic bulbar conjunctiva of the right eye, which revealed features of lipodermoid. Ocular B-scan ultrasonography revealed normal-sized eyeballs with calcification of the right globe. Transfrontal neuro-ultrasound disclosed hydrocephalus and

agenesis of corpus callosum [Fig. 6]. CT scan of the brain and orbit revealed focal calcification of right globe, fatty infiltration in anterior orbit, intracerebral cyst measuring 14×7 cm compressing right ventricle, intracerebral calcification, and lipoma near right cerebello-pontine angle (0.6×0.5 cm) and in right cerebrum measuring 1.2×1.5 cm [Figs. 7 and 8]. Electrocardiography, echocardiography, abdominal ultrasonography, magnetic resonance imaging of spine, and x-ray of the jaw were unremarkable. A chromosomal study (conventional G-banding) showed a normal karyotype (46, XX). The constellation of these



Figure 5: Multiple punched out lesions (focal dermal aplasia) on occipital region of scalp (blue arrows)

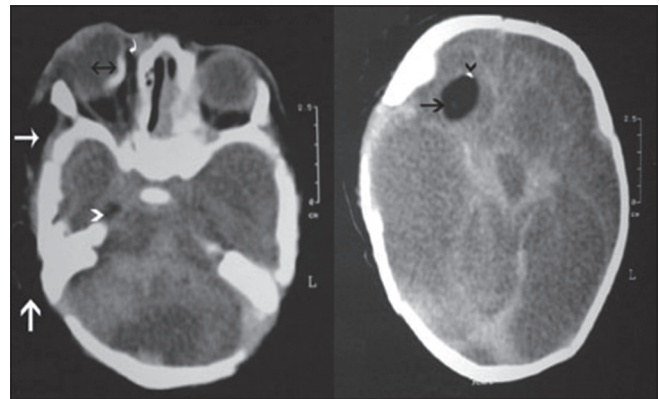


Figure 7: Axial computed tomography of the brain and orbit showing calcification on posterior sclera of the right eye (double arrow), fatty infiltration in anterior orbit (curved arrow), normal sized eyeballs and absence of orbital cyst, lipomas in right temporal region (white arrows), near right cerebello-pontine angle (white arrowhead) and in the right cerebrum (black arrow) with calcification at margin (black arrowhead)

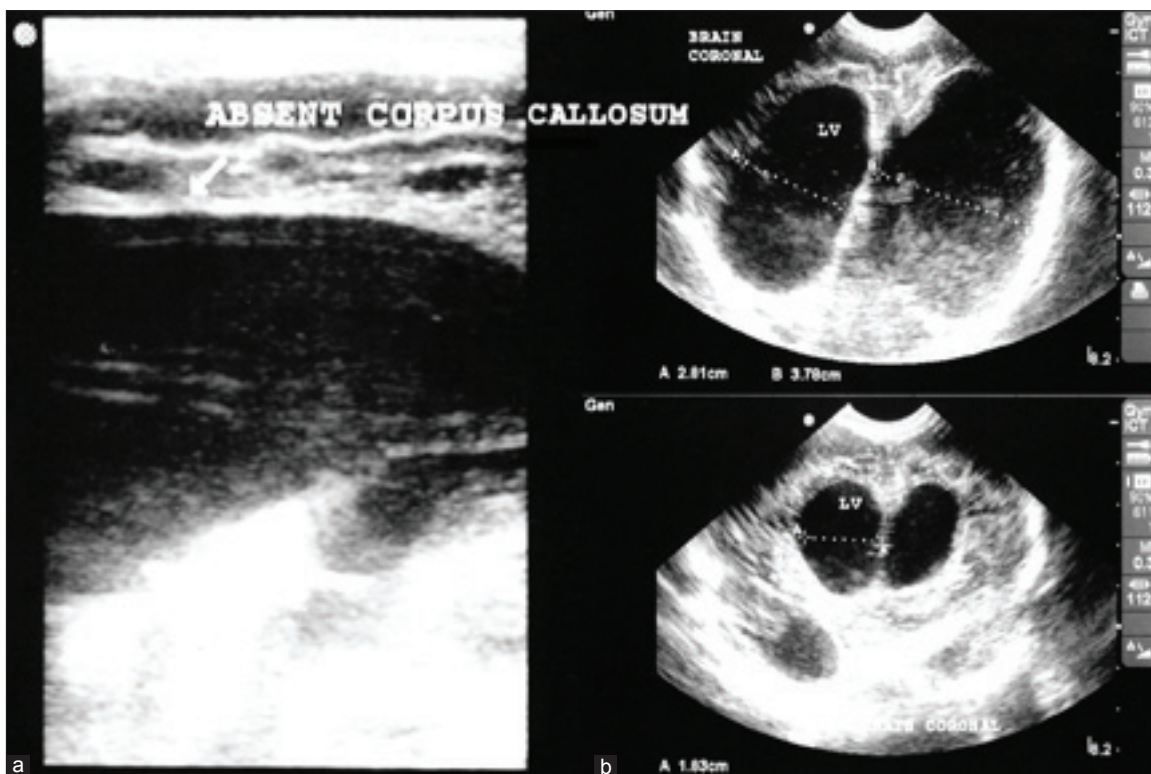


Figure 6: Trans-frontal neuro-ultrasonography of an encephalocraniocutaneous lipomatosis patient showing (a) agenesis of corpus callosum (arrow); (b) dilated lateral ventricles suggestive of hydrocephalus

Table 1: Phenotypic spectrum of Encephalocraniocutaneous lipomatosis^[1-13]

Ocular	Cutaneous	Neurological	Others systems
<p>Typical findings</p> <p>Choristomas (dermoid, epidermoid, lipodermoid), ocular colobomas (eyelid/iris/choroidal/optic disc colobomas), corneal abnormalities (corneal opacities, vascularization), anterior chamber abnormalities, globe calcification,</p> <p>Rare findings</p> <p>Microphthalmos, irregular/sparse eyebrows, ptosis, epicanthus inversus, hypertelorism, strabismus, amblyopia, reduced vision, scleral abnormalities, iris dysplasia, aniridia, glaucoma, cataract, lens capsule dislocation, persistent hyaloid vessels, optic nerve pallor, chorioretinitis, ipsilateral papilledema, retrobulbar tumor, proptosis, orbital cysts</p>	<p>Typical findings</p> <p>Nevus psiloliparus, focal dermal aplasia/hypoplasia on scalp and face, non-scarring alopecia, nodular skin tags, subcutaneous lipoma</p> <p>Rare findings</p> <p>Pigmented melanocytic nevi, hyperpigmentation, capillary hemangioma, hypertrichosis, café-au-lait spots</p>	<p>Typical findings</p> <p>Intracranial lipoma, Spinal lipoma, arachnoid cyst or other abnormalities of meninges, porencephalic cyst(s), seizures, abnormal intracranial vessels, e.g., leptomeningeal angiomas, developmental delay and mental retardation, complete or partial atrophy of a hemisphere, asymmetrically dilated ventricles or hydrocephalus, intracranial calcification</p> <p>Rare findings</p> <p>Cranial asymmetry, macrocephaly, endocranial hypertension, cortical dysplasia or dystrophy, low grade glioma/astrocytoma, papillary glioneuronal tumor, spasticity of contralateral limbs, skull defects</p>	<p>Typical findings</p> <p>Jaw tumor (osteoma, odontoma or ossifying fibroma), congenital heart diseases (coarctation of aorta), multiple bone cysts</p> <p>Rare findings</p> <p>Hydronephrosis, stenotic auditory canal, premature thelarche, hypospadias, single pelvic kidney, spheno-ethmoidal osseous lesions (fibrous dysplasia), infantile spasm, juvenile extra nasopharyngeal angiofibroma of gingiva, coloboma of nasal ala, lipoma in groin, axilla and trunk, bony dysplasia, ventricular septal defect, pectus excavatum, fatty tissue infiltration of heart, nevus sebaceous, epidermal papillomatosis, supraventricular arrhythmia, neurofibromatosis-type-1, hip dislocation, cryptorchidism</p>

Table 2: Moog’s revised diagnostic criteria for encephalocraniocutaneous lipomatosis (ECCL)^[6]

Eye	Skin	Central nervous system	Others systems
<p>Major criteria</p> <p>1. Choristoma, with or without associated anomalies</p> <p>Minor criteria</p> <p>1. Corneal and other anterior chamber anomalies</p> <p>2. Ocular or eyelid coloboma</p> <p>3. Calcification of globe</p>	<p>Major criteria</p> <p>1. Proven nevus psiloliparus (NP)</p> <p>2. Possible NP and ≥ 1 of minor criteria 2-5</p> <p>3. ≥ 2 of minor criteria 2-5</p> <p>Minor criteria</p> <p>1. Possible NP</p> <p>2. Patchy or streaky non-scarring alopecia (without fatty nevus)</p> <p>3. Subcutaneous lipoma(s) in fronto-temporal region</p> <p>4. Focal skin aplasia/hypoplasia on scalp</p> <p>5. Small nodular skin tags on eyelids or between outer canthus and tragus</p>	<p>Major criteria</p> <p>1. Intracranial lipoma</p> <p>2. Intraspinal lipoma</p> <p>3. ≥ 2 of minor criteria</p> <p>Minor criteria</p> <p>1. Abnormal intracranial vessels, e.g., angioma, excessive vessels</p> <p>2. Arachnoid cyst or other abnormality of meninges</p> <p>3. Complete or partial atrophy of a hemisphere</p> <p>4. Porencephalic cyst(s)</p> <p>5. Asymmetrically dilated ventricles or hydrocephalus</p> <p>6. Calcification (not basal ganglia)</p>	<p>Major criteria</p> <p>1. Jaw tumor (osteoma, odontoma or ossifying fibroma)</p> <p>2. Multiple bone cysts</p> <p>3. Aortic coarctation</p>
<p>Application of criteria for the diagnosis of ECCL</p> <p>Definite case</p> <p>1. Three systems involved, major criteria in ≥ 2, or</p> <p>2. Three systems involved, proven NP or possible NP+ ≥ 1 of minor skin criteria 2-5</p> <p>3. Two systems involved with major criteria, one of which proven NP or possible NP+ ≥ 1 of minor skin criteria 2-5</p> <p>Probable case</p> <p>1. Two systems involved, major criteria in both</p> <p>2. Two systems involved, proven or possible NP</p>			

Adopted and modified from: Moog U. Encephalocraniocutaneous lipomatosis. J Med Genet 2009;46:721-9, ECCL: Encephalocraniocutaneous lipomatosis, NP: Nevus psiloliparus

clinical and imaging findings led to a definitive diagnosis of ECCL.

Discussion

Haberland and Perou first described this syndrome in 1970 and coined the term ‘Encephalocraniocutaneous lipomatosis’.^[3] Subsequently, Fishman *et al.* in 1978 and Fishman in 1987 reported three additional cases of ECCL.

Hence, it was also termed as Fishman syndrome.^[4,5] Approximately, 77 patients with the ECCL (PubMed search, accessed on 09-09-2013) have been reported in the literature.^[1-13] No epidemiological data on incidence of the disorder is available. There is no clear gender, racial, or geographical predilection.^[1,2,6]

The pathogenesis of the syndrome still remains unclear. There is no evidence as yet of genetic transmission or

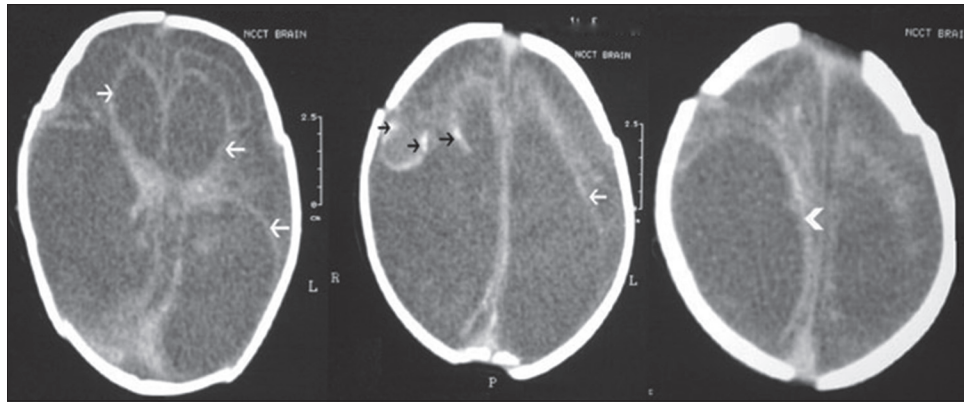


Figure 8: Axial CT scan of the brain showing asymmetrically dilated lateral ventricles (white arrows), multiple intracerebral calcification (black arrows), and intracranial cyst in right cerebrum (arrowhead)

chromosomal abnormality. Somatic mosaicism is thought to be the underlying pathophysiology in ECCL. Dysgenesis of the cephalic neural crest and the anterior neural tube is one of the most widely accepted theory of pathogenesis of ECCL.^[3]

Encephalocraniocutaneous lipomatosis has a very wide and variable spectrum of clinical manifestations.^[1,2] Phenotypic spectrum of ECCL is given in Table 1. Ophthalmia neonatorum in this case seemed to be a coincidental finding.

Sometimes, the diagnosis of the syndrome may be difficult due to absence of any pathognomonic morphological feature or specific molecular marker or laboratory test and its highly variable expressivity.^[1,2,7] Although nevus psiloliparus is a very specific feature of ECCL, it has also been reported independently in non-syndromic patients.^[1,2,8] The diagnosis of ECCL is mainly based on history, clinical examination, and imaging studies. Mac Laren *et al.* in 1995 and Hunter in 2006 have laid down diagnostic criteria.^[2,9] In 2009, Moog proposed revised diagnostic criteria for ECCL.^[1] The Moog's revised criteria for diagnosis of ECCL is shown in Table 2.

Differential diagnosis includes oculocerebrocutaneous syndrome (Delleman-Oorthuys syndrome), nevus sebaceous syndrome, proteus syndrome, Sturge-Weber syndrome, oculo-auriculo-vertebral syndrome (Goldenhar syndrome), neurofibromatosis type-1, focal dermal hypoplasia syndrome (Goltz syndrome or Gorlin-Goltz syndrome), epidermal nevus syndrome (Schimmelpenning syndrome), and oculocutaneous syndrome.^[10] The minimal diagnostic criteria for Delleman-Oorthuys syndrome (oculocerebrocutaneous syndrome) includes a CNS cyst or hydrocephalus, microphthalmia with orbital cyst, and focal dermal hypoplasia or aplasia.^[11] As microphthalmia with orbital cyst was missing from the present case, hence this did not appear to be a case of Delleman-Oorthuys syndrome. In the present case, the right eye has proptosis and mechanical ptosis. This seems to be from conjunctival hypertrophy and lipomatous infiltration of conjunctiva, eyelids, and anterior orbit. However, computed tomography scan did not reveal any space occupying lesion in the posterior orbit.

Many patients with ECCL lead normal lives.^[1,2] Complications related to CNS malformation may be a cause of increased morbidity and mortality in these patients. These patients are also at risk for developing certain neoplasms

such as juvenile extranasopharyngeal angiofibroma of gingiva, papillary glioneuronal tumor, and low-grade glioma/astrocytoma.^[1,2,6,7,10-12] Therefore, screening for these conditions is crucial during follow-up.

A definitive antenatal diagnosis is not possible because intracranial malformations observed on an antenatal sonogram are not specific for ECCL.^[13] There are no effective treatment modalities for ECCL. Ophthalmic management of these cases is limited to excision of choristomas with or without lamellar keratoplasty, removal of cutaneous lesions for cosmetic improvement, and visual rehabilitation. The patient should be followed-up regularly for development of complications and appropriate management.

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