CASE REPORT

Haberland Syndrome (Encephalocraniocutaneous Lipomatosis): A Case Report and Review of Literature

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ABSTRACT

Encephalocraniocutaneous lipomatosis (ECCL), also known as Haberland syndrome, is a rare, nonhereditary, nonprogressive congenital neurocutaneous syndrome with underlying ectodermal dysgenesis. The classic triad of this syndrome is central nervous system (CNS), ocular, and cutaneous involvement as unilateral lipomatous lesions of the scalp, neck, and face with ipsilateral brain anomalies and ipsilateral ocular choristoma. Herein, this study reports a case of a 2-year-old boy presented with status epilepticus for the first time. Intraspinal lipoma, arachnoid cyst, cerebral hemiatrophy, asymmetric hydrocephaly, choristoma, and corneal clouding were noted. This case fulfilled Moog's clinical criteria for diagnosis of Haberland syndrome. Additionally, this study introduces linear and whorled nevoid hypermelanosis and cerebral periventricular white matter hyperintensity as novel manifestations of this syndrome.

Introduction

Haberland syndrome, also known as encephalocraniocutaneous lipomatosis (ECCL) or Fishman disease, is a rare, nonhereditary congenital condition. It was first identified by Haberland and Peru in 1970 as a unique type of neurocutaneous disorder. The syndrome is characterized by its distinct pattern affecting the skin, eyes, and central nervous system (CNS). Symptoms typically include unilateral lipomatous lesions on the scalp and face, lipodermoid lesions in the eyes, and anomalies in the brain on the

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same side of the body (1).

Case presentation:

This case report presents a 2-year-old boy admitted to ICU with focal status epilepticus as jerking his right upper limb for the first time. The parents were non-consanguineous, and all family members, including three older siblings and close relatives, were healthy.

The neurological examination revealed just mild delayed speech development. Two patches of alopecia were noted over flat and softly elevated yellowish-colored areas at the left frontoparietal region. Two small non-tender skin-colored pedunculated nodules were noted at the left eyelid and left lateral epicanthus.

Another mildly raised, firm white-yellow popular lesion was visualized in the limbus and conjunctiva of both eyes. Some hyperpigmented plaques were also noticed in his extremities. These lesions have been present since birth without progression.

A previous ophthalmologic consult had been done one year ago and suggested bilateral corneal clouding and epibulbar lipodermoid lesions. These mentioned findings are demonstrated in (figure 1).

According to a dermatologic consult performed at his admission, hyperpigmented lesions on his limbs were compatible with linear and whorled nevoid hypermelanosis. Periocular skin tags and an elevated patch of alopecia at the scalp, suggestive of nevus psiloliparus, were confirmed. No other remarkable findings were detected in our general examination.

Brain MRI showed atrophy of left temporoparietal lobes ipsilateral to alopecia patches, T1 hyperintense lesion compatible with lipoma located posterior to cervical-medullary junction,

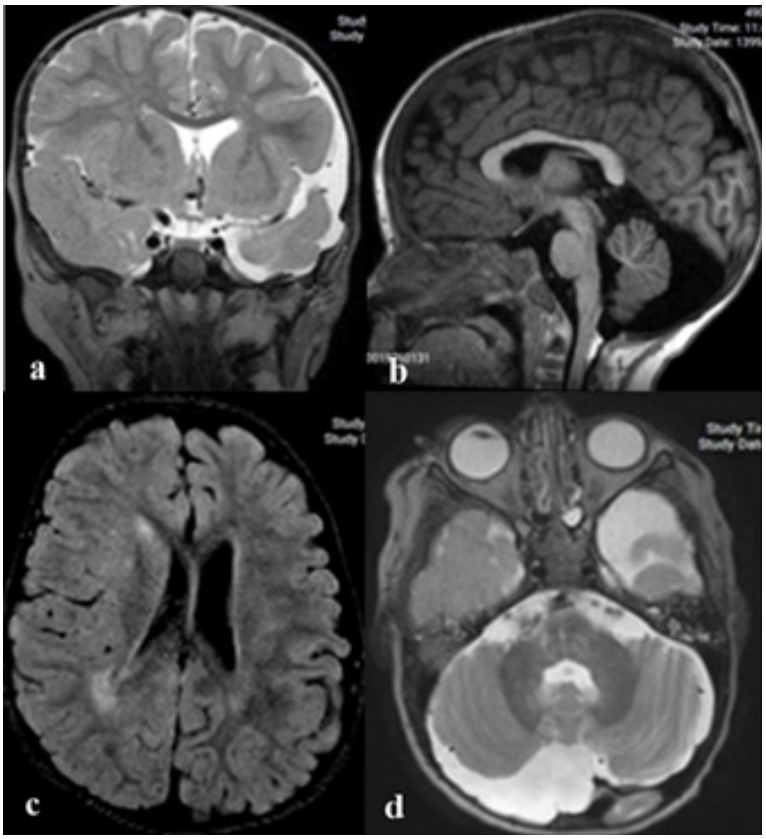

Figure 1. a) Lipodermoid lesions at both eyes. Nodular skin lesions at left lateral epicanthus and left eyelid. b) Patchy alopecia in left frontoparietal region. c) Hyperpigmented macules on right hand

asymmetric size of lateral ventricles associated with mild dilatation of trigone of left lateral ventricle, arachnoid cyst in the left middle cranial fossa and right posterior fossa, hyperintensity of periventricular white matter on long TE MRI sequences and fat-containing cutaneous lesion in the right orbital lateral epicanthus

Lab data tests were all in the normal range.

According to Tables 1 and 2, the clinical and imaging findings fulfill Moog's diagnostic criteria for a definite diagnosis of ECCL.

During his admission, phenobarbital and levetiracetam were prescribed for the patient, and no other episodes of seizure recurred.

Discussion

ECCL is a rare, nonhereditary, nonprogressive congenital neurocutaneous syndrome with underlying ectodermal dysgenesis (1).

CNS, skin, and eyes are the three main organs involved in this syndrome, characteristically as unilateral lipomatous hamartoma of the scalp, neck, and face with ipsilateral brain anomalies and dermolipoma of the eyes. Although unilateral involvement is a predominant feature, cases with bilateral involvement have also been

Table 1. Moog's criteria

	Major	Minor
CNS	• Intracranial lipoma • Intraspinal lipoma • >2 of minor criteria	• Abnormal intracranial vessels (eg, angioma, excessive vessels) • Porencephalic cyst(s) • Asymmetrically dilated ventricles or hydrocephalus • Calcification (not basal ganglia) • Arachnoid cyst or other abnormality of meninges • Complete or partial atrophy of a hemisphere
Eye	• Choristoma, with or without associated anomalies	• Corneal and other anterior chamber anomalies • Ocular or eyelid coloboma • Calcification of globe
Skin	• Proven nevus psiloliparus (NP) • Possible NP and >1 of minor criteria 2–5	• Possible NP • Patchy or streaky nonscarring alopecia (without fatty nevus) • Subcutaneous lipoma(s) in frontotemporal region • Focal skin aplasia/hypoplasia on scalp

Continued Table 1.

	• >2 of minor criteria 2–5	• Small nodular skin tags on eyelids or between outer and tragus canthus
OTHER	• Jaw tumor (osteoma, odontoma, or ossifying fibroma) • Multiple bone cysts • Aortic coarctation	

Table 2. Definite and probable case criteria

Definite case:	• Three systems involved (major criteria) • Three systems involved, proven Nevus psiloliparus (NP) or possible NP + > 1 of minor skin criteria • Two systems involved with major criteria, one of which is proven NP or possible NP > 1 of minor skin criteria
Probable case:	• Two systems involved, major criteria in both • Two systems involved, proven or possible NP

described. Most cases present with neurological manifestation in early childhood, but patients who were first referred with cutaneous or ocular complaints without any neurological symptoms have also been reported(2).

No evidence of race, sex, or geographic predilection was observed. The exact etiopathogenesis of this syndrome is not yet clearly known. The disease occurs sporadically. Somatic mosaicism of a lethal autosomal dominant mutation is a suspected underlying pathology that leads to dysgenesis of the anterior neural tube and cephalic neural crest(3, 4). A group of skin diseases termed 'hypomelanosis of Ito' is believed to share the same genetic inheritance as autosomal dominant mutations surviving with mosaicism.

The diagnosis of ECCL is based on clinical presentation, history, and imaging findings. Hunter proposed the original diagnostic criteria in 2006, which Moog revised in 2009 using minor and major criteria of CNS, ocular, and cutaneous manifestations (Table 1)(2, 5).

Imaging features of CNS involvement are characteristic, including intracranial lipoma, which is the most common finding, cerebral atrophy, ventriculomegaly, ipsilateral to the scalp and ocular lesions, porencephalic and arachnoid cysts, cortical maldevelopment, corticospinal calcification, leptomeningeal angiomatosis, anomalies of the corpus callosum, and spinal intradural lipoma.

Neurological manifestation includes developmental delay, mental retardation, seizures, and spasticity. Seizures usually start in infancy in about half of patients. Their seizures are frequently partial, contralateral to the ocular

and cutaneous lesions, and usually responsive to medication. The patient's mental status varies from normal to severe mental retardation, but no progressive intellectual disabilities were reported. No correlation has been found between the severity of CNS involvement and clinical neurological manifestations.

Ocular involvement includes conjunctival choristoma, the most common ocular manifestation, presenting as a sessile or pedunculated mass from conjunctiva containing dermal and epidermal components. Associated anterior chamber anomalies may be present. Aniridia, colobomas, lens dislocation, clouding of the cornea, microphthalmia, ocular calcifications, and optic disc pallor have been reported.

The most characteristic skin lesion is nevus psiloliparus, a hairless skin-colored or mildly yellowish, flat or raised, fatty tissue nevus that is the hallmark of ECCL. Nonscarring patchy alopecia, skin tags, and subcutaneous lipomas have been commonly reported. Melanocytic nevi is another less common skin lesion found in these patients (5, 6).

Other associated anomalies that have been reported are jaw tumors, bone cysts, ossifying fibroma, osteoma, and aortic coarctation.

Other neurocutaneous syndromes are differential diagnoses, including Proteus syndrome, Sturge-Weber syndrome, epidermal nevus syndrome, neurofibromatosis, Oculocerebrocutaneous syndrome/Delleman syndrome, and Goldenhar syndrome.

Proteus syndrome, the closest differential diagnosis, is a rare progressive multisystemic disease characterized by hamartomatous lesions and asymmetric overgrowths of body parts. Patients are normal at birth. Epidermal nevus is specific for this disease. The most common CNS manifestation in Proteus syndrome is hemiplegancephaly.

Characteristic CNS and cutaneous manifestations distinguish these disorders from ECC (6).

Prenatal diagnosis of ECCL is not possible because of nonspecific sonographic findings. However, early diagnosis could improve the quality of life by treating patients' symptoms(7).

Some major and minor features were detected in the studied patient, including arachnoid cyst, cerebral hemiatrophy, intraspinal lipoma, asymmetric hydrocephaly, choristoma, corneal clouding, patchy alopecia, and skin tags.

According to the abovementioned criteria, our diagnosis was compatible with a definite diagnosis of Encephalocraniocutaneous lipomatosis (Table 3).

The parents refused to perform tissue biopsy or genetic testing.

Most patients have a normal life expectancy, morbidity, and mortality, which are related to CNS complications, the increased risk of spinal anomalies, and some neoplastic conditions like low-grade glioma, papillary glioneuronal tumor, astrocytoma, and juvenile extranasopharyngeal angiofibroma of the gingiva. Therefore, follow-up of these patients is necessary (7, 8).

Treatment is symptomatic, like anticonvulsant drugs for patients with seizures and cosmetic surgery for cutaneous and ocular lesions (9).

This syndrome's major CNS and ocular features were found in the studied patient, including intraspinal lipoma, arachnoid cyst, cerebral hemiatrophy, asymmetric hydrocephaly, choristoma, and corneal clouding. Nevus psiloliparus, a hallmark of cutaneous manifestation, was not detected, but other minor skin lesions, like patches of alopecia and skin tags, were present.

Linear and whorled nevoid hypermelanosis have not been previously described in cases of ECCL. These lesions are hyperpigmented macules in a linear configuration, mostly on the trunk and limbs, found in the left forearm and hand in the studied case. They are usually detected in the first weeks of life. Associated chromosomal abnormalities and extracutaneous manifestations, such as skeletal, cardiac, ocular, and neurological involvement, are commonly seen. Genetic studies suggest mosaicism is a common cause of the possible background etiology of ECCL(10).

Cerebral periventricular white matter hyperintensity detected in the contralateral hemisphere in the studied patient has not been reported previously and could suggest some degree of white matter dysmyelination concomitant with other cerebral anomalies.

In conclusion

we should be aware and look for other clinical and imaging findings in patients
with definite or suspected diagnosis of Haberland syndrome, including white matter
abnormalities and linear and whorled nevoid hypermelanosis as in our case.

Acknowledgment

The parents of patient in this case report signed informed consent. The context of the consent forms included that the patient's images and clinical information would be reported in a journal without mentioning his/her name.

Authors' Contribution

Ala Torabi: Conceptualization, Data acquisition, Writing and editing the manuscript

Neda Pak: Conceptualization, Data acquisition, Editing the manuscript, Supervision

Reza Shervin Badv: Conceptualization, Data acquisition

Masoud Mohammadpour: Conceptualization, Data acquisition

Fatemeh Zamani: Conceptualization, Data acquisition

Masoumeh Sadat Sadeghzadeh: Conceptualization, Data acquisition

Conflict of Interest

The authors declared no conflicts of interest.

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The genetic mechanism has been hypothesized to involve lethal autosomal dominant genes that survive by mosaicism, and the pathogenesis is most likely a dysgenesis of the cephalic neural crest and anterior neural tube