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► **To cite this version:**

Ute Moog. Encephalocraniocutaneous Lipomatosis. Journal of Medical Genetics, 2009, 46 (11), pp.721. 10.1136/jmg.2009.066068 . hal-00552691

HAL Id: hal-00552691

<https://hal.science/hal-00552691>

Submitted on 6 Jan 2011

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Encephalocraniocutaneous Lipomatosis

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Keywords: encephalocraniocutaneous lipomatosis; intracranial lipoma; neural crest disorder

Word count: 3362

ABSTRACT

Background: Encephalocraniocutaneous lipomatosis (ECCL) is a sporadically occurring neurocutaneous disorder of unknown aetiology. It has repeatedly been discussed as a localised form of Proteus syndrome. In 2006, the first larger series of patients has been reported by Hunter and diagnostic criteria have been proposed.

Aims: To better define the phenotypic spectrum and natural history of ECCL and to revise diagnostic criteria.

Methods: 54 patients with ECCL have been reviewed.

Results: Eye anomalies (mainly choristomas) and skin lesions (non-scarring alopecia, nevus psiloliparus, subcutaneous fatty masses, nodular skin tags, aplastic scalp defects) may be uni- or bilateral and occur in a consistent pattern. CNS anomalies consist of intracranial and intraspinal lipomas, congenital abnormalities of the meninges, and putative focal vascular defects resulting in highly asymmetrical changes. About 2/3 of patients have a normal development or mild retardation only, and half of them have seizures. A correlation between the extent of CNS anomalies and neurological features could not be established. Aortic coarctation, progressive bone cysts and jaw tumours may be associated.

Conclusions: Revised diagnostic criteria are proposed. ECCL is considered to differ in particular from Proteus syndrome, but oculoectodermal syndrome is possibly a mild variant. Pathogenetically, mosaicism for a mutated autosomal gene involved in multiple mesenchymal tumours and vasculogenesis, with or without a second hit event is discussed.

INTRODUCTION

Encephalocraniocutaneous lipomatosis (ECCL) is a sporadically occurring neurocutaneous syndrome characterized by the presence of skin lesions, ocular and CNS anomalies. The first case was reported in 1970 by Haberland and Perou.[1] They also coined the term encephalocraniocutaneous lipomatosis which refers to the major features and was generally adopted despite the intervening name of Fishman's syndrome after the publication by Fishman et al. in 1978.[2] The majority of patients have been reported under the term encephalocraniocutaneous lipomatosis, although publications under other terms from the ophthalmologic literature, as well as under terms resulting from misdiagnoses, are known.

In the literature, including well-known text books, ECCL has repeatedly been described as a rare disorder with unilateral and mostly severe manifestation, probably representing a localised form of Proteus syndrome.[3,4] In 2006, Hunter reviewed the first larger series of patients, proposed diagnostic criteria, and identified 29 patients with a definite diagnosis.[5]

This paper gives an up-date review on ECCL and contributes to a new understanding of this syndrome.

METHODS

54 cases of ECCL are reviewed. These include 27 of the 29 cases classified as definite by Hunter.[1,6,7;8, Pat.1;9-28] Two of Hunter's definite cases have been excluded from review: Patient 2 of Bamforth [8] has not been listed separately as this patient has been published previously by Fishman [14] and included as such in the Table. The paper by Saraux and Offret deals in a broader sense with syndromic choristomas and includes a patient illustrated by figures and interpreted as having ECCL; however, data provided on this patient were considered insufficient to establish a reliable diagnosis of ECCL.[29]

In contrast, 4 patients who, according to Hunter's criteria, showed insufficient signs, or had probable or uncertain diagnoses, have been included.[30-33] For one of them, follow-up data could be obtained [30, follow-up in 34]; in another, the association with jaw tumours made the diagnosis very likely [32]; in two patients, the overall picture and presence of a likely nevus psiloliparus justified the inclusion.[31,33]

In addition, 23 further patients have been reviewed, all of whom meet Hunter's criteria except one patient who has been included because of his typical skin lesions.[34-45;46, Pat.2;47-53]

RESULTS

Results are summarised in Table 1, and in Table 2 which is available in the online version of *Journal of Medical Genetics*.

Skin anomalies

Non-scarring alopecia, with or without underlying fatty tissue, and subcutaneous fatty masses, are the most important skin anomalies. A smooth, hairless fatty tissue nevus of the scalp, the so-called nevus psiloliparus (NP), has been confirmed as the dermatologic hallmark and found in 44 out of 54 patients (fig 1). The NP was recognised by Happle & Küster in 1998, and was thought to be pathognomonic until two otherwise healthy girls with isolated NP were described.[54,55] These, however, underwent no neuroimaging studies. Alopecia without a fatty nevus can be linear or patchy, and may follow the lines of Blaschko (fig 2). Some patients have scarring alopecia resulting from focal skin aplasia (fig 3); this was observed in 14/54 patients. Focal aplastic or hypoplastic skin defects other than those on the scalp are very rare. Typically subcutaneous fatty masses are seen in the frontotemporal or zygomatic region (21/54), and may be uni- or bilateral (fig 4, 5, 6). Rarely, subcutaneous lipomas are seen outside the craniofacial region. In addition, small nodular skin tags can be found (40/54), most often on the eyelids or following a line from outer canthus to tragus (39/40) (fig 5, 6). Histologically, they are fibromas, lipomas, fibrolipomas or choristomas. Excluding the patient with a concomitant NF1 diagnosis, three patients had several café-au-lait spots. Interestingly, one patient showed hyperpigmentation following the lines of Blaschko and also leg asymmetry.[44, Pat.2] A 17 month-old girl showed association of ECCL and neurocutaneous melanosis with small congenital melanocytic nevi involving 70% of the body surface. On histological examination, these were atypical nodular proliferations of dermal nevomelanocytes. Nevomelanocytes were also found in the villi of the placenta.[35]

Ocular anomalies

Choristomas, with or without other eye anomalies, are seen in the majority of patients (43/54) (fig 5). These are benign ocular tumours and include epibulbar or limbal dermoids (dermolipomas) derived from epidermis and dermis, and lipodermoids which consist mainly of fat and rarely decrease vision.[5] Dermolipomas however can be associated with significant anomalies, including corneal and scleral anomalies, other anterior chamber abnormalities, ocular and palpebral colobomas (fig 6), aniridia, microphthalmia and calcification of the globe. Interestingly, most of the patients without choristomas had one or more of the associated lesions. Another interesting finding is irregular or disrupted eyebrows observed in five patients (fig 6).

Taken together, 40% of patients (22/54) showed bilateral abnormalities of the skin and/or the eyes. Although variable in its extent and severity, the pattern of skin and eye findings was found to be very consistent and recognisable.

Neurology

The spectrum of neurological features is very broad and comprises: patients with normal development and without seizures; patients with normal development but suffering seizures that can be refractory or may even require neurosurgery; patients with mental retardation of varying degrees; and children presenting with a severely disabling disorder with deep psychomotor retardation, intractable seizures and several other physical problems.

Developmental data could be found for 45 patients. Of these, 13 developed normally up to a reported age ranging from 3 months to 24 years (mean 7 years), 16 showed mild retardation, and 16 moderate to severe or unspecified retardation.

27 patients had history of epileptic seizures and three did not; in 24 patients no information was given if seizures occurred or not. Of the 27 patients with seizures, in nine patients the onset of seizures was during the first month of life, in seven patients during the

first year, in six patients above the age of one year, and in five patients no documentation was given. Eight out of 27 patients suffered from refractory epilepsy and in a further six, the seizures were at least difficult to treat. In 13 patients, seizures responded well to anti-epileptic treatment.

CNS anomalies

Recently, the CNS anomalies in ECCL have been reviewed in detail.[34] The neuroimaging findings of the present 54 patients can be viewed in the online version of *Journal of Medical Genetics* (Table 2). Lipomas were the most prominent feature, and found on neuroimaging in 33 out of 54 patients. Intracranial lipomas (31/55) were often located in the cerebello-pontine angle (19/31) which is exceptional because in general, lipomas are more frequently found between the hemispheres.[56] Spinal lipomas were found in most of the patients when looked for (12/14), and can extend over the whole length of the spinal cord. It is therefore recommended that a spinal MRI is performed when ECCL is suspected. Subcutaneous fatty masses may overlie the spinal lipomas, or be found next to the spinal cord. No other cranial or spinal tumours were found, except in one patient who had a concomitant diagnosis of NF1.[30]

In addition, congenital abnormalities of the meninges were seen, in particular archnoid cysts documented in 21 patients.

Furthermore, highly asymmetric changes were found, consisting of complete or partial atrophy of a hemisphere, porencephalic cysts, dilated ventricles or hydrocephalus, and calcifications. It has been proposed that all these may result from focal vascular defects. Vessel anomalies including leptomenigeal angiomas, abnormal or excessive vessels, were seen in 10 patients. This is of particular importance as probably only a small proportion of patients had undergone studies appropriate for detecting vascular anomalies.[5]

The extent of intracranial lesions corresponds neither to the degree of possible retardation or epilepsy, nor to the extent of skin and eye findings. Prognoses thus can not be based on neuroimaging findings.

Associated findings

Skeletal anomalies

11/54 patients were macrocephalic. Jaw tumours have been documented in another 6 patients and were identified as osteomas, odontomas or ossifying fibromas.[18,7,32,53,26,44] These may be progressive. Three patients with a severe form of ECCL developed multiple lytic bone lesions. In one patient it was spreading all over the skeleton; in another patient histology showed non-ossifying fibromas (fig 7).[44]

Congenital heart defects

Congenital heart malformation was diagnosed in 5 out of 54 patients, in particular aortic coarctation (4/5).

Other

Two patients showed hypospadias,[46, Pat.2;34, Pat.2] one a pelvic kidney and two hydronephrosis.[44] One patient had a stenotic auditory canal [49] and another premature thelarche.[8, Pat.1]

Diagnostic criteria for ECCL

Regarding the existing diagnostic criteria for ECCL set up by Hunter in 2006, the findings in the present 54 patients confirm that choristoma and NP are major criteria and that NP has an outstanding role as criterion. A modification seems appropriate with regard to the significance of intracranial and intraspinal lipomas, and the specification of other brain anomalies. As jaw

tumours, bone cysts and aortic coarctation are infrequent but highly specific features, a fourth system of associated anomalies can also be added. Table 3 comprises the revised and slightly simplified diagnostic criteria. As in practice, a distinction between proven, probable and possible NP/compatible findings of NP may be difficult to reach, NP's are categorized just as proven and possible.

In contrast to the original criteria, a NP plus a minor criterion in a second system is regarded insufficient to establish a definite diagnosis of ECCL but satisfies a probable diagnosis. This may of course change if NP is shown to be a pathognomonic sign in the future. For the time being and as long as the molecular basis of ECCL is unknown, strict criteria are preferred. The four patients with non-definite diagnoses following Hunter's criteria that have been included in this review meet the criteria for a definite diagnosis following the revised criteria. In contrast, two other patients satisfy the criteria for probable diagnoses only; one had manifestations that are atypical for ECCL,[35] and the other did not meet Hunter's criteria for a definite diagnosis either.[51]

The differential diagnosis of ECCL

Proteus syndrome

ECCL has been repeatedly discussed as a localised form of Proteus syndrome (PS).[3,4,57] However, ECCL does not meet the criteria established for PS.[58] To make a diagnosis of PS, the general criterion of progressive course must be satisfied. In ECCL, signs in general are present at birth and non-progressive. Exceptions are possible skeletal cysts and jaw tumours. In addition, one patient was shown to have intracranial vascular lesions at the age of one year which were not present in the neonatal period,[2, Pat.1;14, Pat. 2] and another patient developed marked hydrocephalus at 7 months which was absent at birth but could be a secondary feature.[12] With regard to the specific criteria for PS, a cerebriform connective tissue nevus and epidermal nevus are not part of ECCL and clearly different from a NP.

Hyperostoses of the skull, dysregulation of adipose tissue and vascular malformations are part of both syndromes yet different. Hyperostoses of the skull are signs of disproportionate, progressive and distorting overgrowth in PS but they are non-progressive and underlie areas of alopecia or NP's in ECCL. Dysregulation of adipose tissue occurs in four types in PS: lipomas, lipohypoplasia, fatty overgrowth and localised fat deposits/partial lipohyperplasia.[57] In ECCL, intracranial and spinal lipomas, NP's on the scalp, and subcutaneous fatty masses, in particular in the frontotemporal region, can be seen. Again, these fat deposits are non-progressive, but may become larger in concert with general growth. Very rarely, visceral involvement can be observed.[1;34, Pat.2] Thus, lipomas are seen both in PS and ECCL but are clinically different and without other signs insufficient finding to satisfy the criteria for PS. The vascular malformations in PS are capillary, venous, lymphatic or combined malformations; intracerebral vessel anomalies as seen in ECCL are no typical finding in PS. Epibulbar dermoids - which are much more frequent and a major criterion in ECCL - and the lytic bone lesions are findings in both syndromes but not part of the PS diagnostic criteria .[44]

Three patients have been reported as having overlapping phenotypes of ECCL and PS, and have been repeatedly cited.[59-61] Two were excluded from having ECCL by Hunter and also do not meet the revised criteria for ECCL.[59,61] The third one is an uncertain case of ECCL with atypical skin lesions.[60, Pat.3] In none of the three, the criteria for PS are clearly met.

Based on existing diagnostic criteria and on patients reported as having so-called overlapping phenotypes, there is thus insufficient reason to classify ECCL as a localised form of PS, and both syndromes are considered separate entities.

Oculoectodermal syndrome

Oculoectodermal syndrome (OES) shows a striking resemblance to ECCL with regard to the ocular and skin features; it has recently been proposed to represent a mild variant of ECCL.[62] 15 patients have been reported to date. The most characteristic signs are epibulbar dermoids, focal aplastic skin defects and non-scarring alopecia of the scalp.[62] One patient had a probable NP. Craniofacial lipomas are rarely seen, but one patient showed the typical subcutaneous fatty masses over the zygoma. A major difference is the lack of intracranial lipomas, but only 9/15 patients underwent brain imaging, and none had a spinal MRI. Skeletal cysts and jaw tumours have been described in several less severely affected patients; aortic coarctation has been reported in one patient who also presented with bladder exstrophy.

Oculocerebrocutaneous syndrome

Like ECCL, oculocerebrocutaneous syndrome (OCCS) is characterized by a trias of congenital brain, eye and skin anomalies predominantly affecting the craniofacies. Focal aplastic or hypoplastic skin lesions and microphthalmia occur in both syndromes. However, the most typical cutaneous signs are NP in ECCL versus a post-auricular almond shaped hypoplastic skin defect in OCCS; ocular hallmarks are epibulbar dermoids and cystic microphthalmia, respectively.[5] The brain anomalies in ECCL, which primarily affect the tissue surrounding the brain and the vessels, are very different from the characteristic pattern of primary brain malformations seen in OCCS. The latter consist of frontal predominant polymicrogyria, with or without periventricular nodular heterotopia; of agenesis of corpus callosum that may be associated with variable midline cysts; of asymmetrically enlarged lateral ventricles or hydrocephalus; and of a unique malformation of the mid-hindbrain consisting of a dysplastic, giant tectum and the complete absence of the cerebellar vermis.[63] The cause is still unknown, but OCCS is probably non-mosaic and may be X-linked.[63]

Epidermal nevus syndromes

Epidermal nevus syndromes (ENS) are a group of mosaic neurocutaneous conditions of unknown aetiology, characterized by epidermal nevi following the lines of Blaschko and congenital anomalies involving the eye, CNS, skeleton and other systems. The eye findings in ECCL and ENS can be similar; they include choristomas, coloboma and extension of epidermal nevi to involvement of eyelid or conjunctiva in ENS.[4] In a recognizable neurologic variant of ENS, hemimegalencephaly and gyral malformations are the predominant brain anomalies, but blood vessel anomalies, atrophy, porencephalic cysts, and calcifications as well as intracranial and spinal lipomas also occur.[64,65] Also patients with less characteristic CNS involvement can show spinal lipomas.[66] Skeletal defects are seen more often than in ECCL, and include focal bone lesions.[67] So far, the main differential criteria are the skin lesions which are complex in ENS, and include different forms of epidermal nevi which change over time.

Aetiology and pathogenesis of ECCL

The current knowledge on the phenotype of ECCL, summarised above, allows preliminary conclusions about its aetiology and pathogenesis.

Both males (32) and females (22) are affected, and so far no recurrence in siblings or offspring has been reported. Most of the tissues affected in ECCL are neural crest derivatives, i.e. the meninges and cranial vessels (cranial and spinal lipomas, anomalies of the meninges, vessel anomalies and vascular defects), dermis and hypodermis of face and neck (NP, scarring and non-scarring alopecia, subcutaneous fatty masses), head mesenchyme (choristomas), dermal bones of the skull (protuberances), truncoconal septum and aortic arch (coarctation and other heart defects), odontoblasts (odontomas), and melanocytes (melanosis in one patient [35]). In addition, other bones and fatty tissue than those of the head and face, may be involved; these are derived from the mesoderm. ECCL thus is a mesenchymal disorder affecting in particular neural crest derivatives. There is also evidence that there is no primary structural brain

malformation, but that all CNS anomalies are caused by a mesenchymal defect affecting the tissues surrounding the brain or the vessels.[34] The timing probably is restricted to a narrow window during embryogenesis.

The defect gives rise to multiple benign and mostly mesenchymal tumours: to lipomas, choristomas, odontomas, osteomas, ossifying fibromas, and to bone cysts (identified as non-ossifying fibroma in one case). Among these, jaw tumours and bone lesions may be progressive, whereas the others are present at birth and are non-progressive. In addition, vascular defects can be seen, in particular aortic coarctation and anomalies of intracranial vessels. It has therefore been proposed that a gene involved in vasculogenesis and in the development of multiple mesenchymal tumours, comparable to the architectural transcription factor *HMG2A* may be involved in the aetiology.[44]

Strikingly, one patient had a concomitant diagnosis of NF1 with a proven *NF1* mutation and three other patients showed multiple café-au-lait spots. Two patients had dysplasia of the sphenoid wing which is a skeletal lesion observed in NF1. The question is whether ECCL is a genetic tumour syndrome aetiologically related to NF1. Legius et al., who described the patient with both ECCL and NF1, hypothesised that ECCL may result from somatic mosaicism for a 2nd mutation in the normal NF1 allele or in another unrelated gene.[30] A second hit in another gene of the RAS-MAPK pathway is conceivable.

Because of its sporadic occurrence, and the patchy skin and bone lesions, ECCL has often been considered as a mosaic condition. The hyperpigmentation associated with leg asymmetry in one patient, and the linear alopecia in others, both following the lines of Blaschko strongly support the idea of mosaicism. On the other hand, there is a striking homogeneity of the craniofacial pattern, and of tissues and regions involved. So far, it is still unknown whether ECCL results from a mosaic heterozygous mutation, or from heterozygous mutations and a somatic second hit leading to a mosaic biallelic mutation.

In conclusion, ECCL presents as a disorder different from PS with a consistent and recognisable pattern of uni- or bilateral skin and eye anomalies, a multitude of mesenchymal tumours, in particular lipomas, and choristomas, and CNS anomalies resulting from defects of the meninges and the vessels. The neurodevelopmental spectrum is broad, with a normal development or mild retardation seen in roughly 2/3 of patients. Aetiologically, mosaicism for a mutated autosomal gene involved in multiple mesenchymal tumours and vasculogenesis, with or without a second hit event, is likely.

Competing interests: None declared

Patient consent: Obtained

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FIGURE LEGENDS

Fig 1: Nevus psiloliparus: a smooth hairless fatty tissue nevus on the scalp.

Fig 2: Linear alopecia following the lines of Blaschko (photograph submitted with written consent from the patient's legal guardian for publication in print and online). Note also the subcutaneous fatty mass and small nodular skin tags, both extending to the outer canthus.

Fig 3: Focal skin defects with alopecia on the scalp (scarring alopecia).

Fig 4: Note bilateral subcutaneous fatty accumulations in the temporal region (photograph submitted with written consent from the patient's legal guardian for publication in print and online) .

Fig 5: Epibulbar dermoid of the left eye (photograph submitted with written consent from the patient's legal guardian for publication in print and online). Note also subcutaneous fatty mass in the left temporal region.

Fig 6: Disrupted eyebrows, nodular tag on and coloboma of the left upper eyelid, subcutaneous fatty mass in the right temporal region (photograph submitted with written consent from the patient's legal guardian for publication in print and online).

Fig 7: Multiple lytic bone lesions in the humerus.

Table 1. Clinical features of 54 patients with ECCL.

Ref./ Pat. #		Skin						Eyes				Neurology			Other	
Ref.	Sex/ Age	Uni-/ Bilat.	NP Alop.	Subc. lipom	Hypo Aplas	Tags	Other	Uni-/ Bilat.	Chor.	Assoc. anom.	Other	MR/DD	Seizures	Other	Skeletal	Vessels/ Heart
35	F, 17m						1	UR	+		13, 14	++	+++ w		CA	
6	M, 17y	B	NP	a		e		B	+	g, i		+++	+++ w	S	M, CA	
36	M, 6m	B	NP	a, c		e		B	+	i, k	15	+	-	S		
37	M, 3y	UR	NP FA					UR	+			+	++ m	S		CV
7	M, 9y		NP				CAL, 2	UL	+		14, 16	-	-	25	J	
8.1	F, 4.5y	UL	NP	a		d, e		UL	+				++ w	P	BP, CA	
8.2 14.3	F, 14y 40y*	UL	NP			d, f	CAL	UL	+	g,i		+	++ y	26	M, CA, 27	CV
9	F, 4m	UR	NP SA	a		d, f		B	+		14, 17	++	+			
10	M, 23y		NP			e, f	3	B	+	i		-			CA	
11	F, 0m	UR	NP			d, e, f		UR	+							
12	F, 7m	UR	FA		A			B	+	i, m		+++			M	
13 15	M, 9y	UL	NP	a	H			UL		i	18	+				
38	F, 24y	UL	NP					UL	+	i		-	+++ m			CV
2.1 14.2	M, 15y	UL	NP			d		UL	+	h	14	+	++ w	S	M, BP	CV
2.2 14.1	M, 20m	UR	NP			d, f		UR	+			+	+ m	S	M, BP	
39	M, 13y	B	FA	b		d, f	4	UL	+			++	+ y			
16	M, 11m	B	NP	a	A	d, f		UR	+		19	-			M	

Ref./ Pat. #		Skin						Eyes				Neurology			Other	
1	M, 5y	B		a, b		d		UR	+			+++			BP	F, CV
17 34.8	M, 17 y	UR	NP					UR	+	g		+	+		BP	
18	M, 7y	UL	NP	a		f		UL	+			-			J	CV
19 34.10	F, 17y	UL	NP		A, H		5	UL	+	l, m	19				M, CA	
20	M, 1y	UL	NP	a		e		UL	+	g		+				
41	F, 6y	UR	NP			d		UR	+			++	+ y			
42	F, 3y	UL	NP	a, c		d		B		h, i		-				
30 34.9	M, 12y	UL	NP*				CAL, 6	UL		g			+	NF 1		
31	F, 1y	UR	NP	b	H	d, e		UR	+	l, n		++	++ w	P	BP, SD	
43	M, 0m	UR	FA			d, e		B	+	g						CV
32	M, 9y		FA				7	B	+			-			J	
33	M, 1y	UR	NP FA			d, f		UR		g		++	+	S		
44.1 45.2	M, 10y	B	NP	a	A	d, f		B	+	l, m	17	+++	+++ w		Cysts	COA**
44.2	M, 5y	B	NP			d	Bl	B	+	g, l	17	+++	+++ w		Cysts	COA
44.3	M, 9y	B	NP	a	A	d		B		h, m	17, 14	+++	+++ y		Cysts	COA
34.1	M, 22m	B	NP	a, b		e		B	+	g	15, 20	+			M	
40 34.2	M, 3y	B	NP			d		B	+	g, h, i, k	21, 13	+++	+ m			F
34.3	F, 2y	UL	SA	a		d, e	Bl	UL	+	i		-			J, CA	
34.4	M, 15y		NP	a			8	UL	+	g, m	21, 19	+	+ w	Psy	M, PE	VSD
21	F, 2y		NP SA	a, c		d				n	17	-			BP	CV

Ref./ Pat. #		Skin						Eyes				Neurology			Other	
22	M, 11m	U L	NP SA	a	H	d	9	U L	+	i, l			+ m			
23.1	M, 7y	U R	NP FA			d		U R	+	n	19	+	+ y	P		CV
23.2	M, 2y	U R	NP					U R	+			-				
46.2	M, 8y		NP FA		H, A	d	10	B		m, g	22	+	++ y	Psy	M	COA
47	F, 7m	B	FA			e	CAL 11	B	+	g						
24 50.2	F, 9y	U L	NP SA			d, f						-		Psy	M	
48	F, 0m	B	NP	a	A	d, f		B	+		13					
49	M, 14y	U L	NP FA	b, c			12	U L	+			++	+ m	31	CA	
25	F, 2y	B	NP FA	a	H	d, e, f		B	+			+	+++ m	S		
26	F	U R	FA			d, e		U R	(+)	m, n, h	23	+		P	J	
50.1	F, 1y	U R	NP			d, f		U R	+			-	+ w			
51	M, 2m	U L	NP SA	a	A	d	Bl					++				
27.1	F, 3m	U R	NP		A	d, f						-	-			
27.2	M, 2m	B	NP FA, SA		A	d		U R	+		24	++			CA	
52	M, 0m	B	NP FA			d, e		B	+							CV

Ref./ Pat. #		Skin						Eyes				Neurology			Other		
28	F, 8m	U	NP			d, e		U	+	g, i	13	+				HD	
53	F, 21y	U L	FA	a				U L	+	i		+	+++			J, CA	
Ref.	Sex/ Age	Uni-/ Bilat.	NP Alop.	SFM	Hypo Aplas	Tags	Other	Uni-/ Bilat.	Chor.	Assoc. anom.	Other	MR/DD	Seizures	Other	Skeletal	Vessels/ Heart	

Legends: M: Male, F: Female, U: Unilateral, B: Bilateral, R: Right, L: Left, *: personal communication, +: present, -: reported to be absent

Skin: NP: Nevus psiloliparus, Alop.: alopecia, FA: focal alopecia, SA: streaky alopecia; Subc. lipom.: subcutaneous lipoma, a: frontotemporal, b: epi-/paraspinal, c: other localisation; H: hypoplasia, A: aplasia; Tags: d: on eyelid, e: on area between outer canthus and tragus, f: other site
Other: Bl: skin lesions following lines of Blaschko, CAL: café-au-lait spots; 1: cong. melanosis, hypertrichosis, naevus sebaceous; 2: angiofibroma of gingiva; 3: suprapubic fat pad; 4: lipoma in R axilla and on trunk; 5: coloboma L nasal ala; 6: large pigmentation L shoulder; 7: lipoma in groin; 8: irregular granular pigmentation; 9: capillary hemangioma; 10: pigment changes on the back, chest and abdomen (Ito); 11: nevus sebaceus L scalp, verrucous nevus on the neck; 12: epidermal papillomatosis on face and neck, soft masses over oral mucosa and tongue

Eyes: Chor.: choristoma, Associated anomalies: g: corneal anomalies, h: anterior chamber anomalies, i: ocular colobomas, k: aniridia, l: palpebral coloboma, m: microphthalmia, n: calcification of globe

Other: 13: (chorio-)retinal lacunae; 14: eyelid anomalies incl. ptosis; 15: glaucoma; 16: strabismus; 17: irregular/sparse eyebrows; 18: chorioretinitis; 19: hypertelorism; 20: cataracts; 21: hyperplasia primary vitreous; 22: orbital cysts; 23: retrobulbar tumour; 24: abnormal papilla;

Neurology: MR: mental retardation, DD: developmental delay, -: no MR/DD, +: mild MR/DD, ++: moderate or unspecified MR/DD, +++: severe MR/DD; Seizures: +: well controlled or not further specified, ++: severe or change of medication necessary, +++: refractory, seizures under medication, w: onset within first 1-4 weeks of life, m: onset within 1-12 months of life, y: onset later than age 1y

Other: S: spasticity, P: paresis, Psy: psychiatric disease, 25: Hearing loss, 26: 2-3 strokes, sleep problems, panic attacks, psychogenic seizures?

Other: Skeletal: BP: bony protuberance, CA: cranial and/or facial asymmetry, HD: hip dysplasia, J: jaw tumour, M: macrocephaly, PE: pectus excavatum, SD: skull defect, 27: dysplasia sphenoid wing and temporal bone L

Vessels: COA: coarctation of the aorta, **: with hypoplasia of thoracic aorta, CV: cranial vessels anomalies, F: fat tissue infiltrating the heart, VSD: ventricular septal defect

References: 35 Ahmed et al., 2002; 6 Alfonso et al., 1986; 36 Almer et al., 2003; 37 Amor et al., 2000; 7 Andreadis et al., 2004; 8 Bamforth et al., 1989 ; 9 Brown et al., 2003; 10 Chittenden et al., 2002; 11 Ciatti et al., 1998; 12 Cultrera et al., 2004; 13 Deda et al., 2001; 38 Donaire et al., 2005; 2 Fishman et al., 1978; 14 Fishman, 1987; 15 Fitoz et al., 2002; 39 Gokhale et al., 2007; 16 Grimalt et al., 1993 ; 1 Haberland & Perou, 1970; 17

Happle & Steijlen, 1993; 18 Hauber et al., 2003; 19 Hennekam, 1994; 40 Jones, 2006; 20 Kodsi et al., 1994; 41 Koishi et al., 2008; 42 Lasierra et al., 2003; 30 Legius et al., 1995; 31 Loggers et al., 1992 ; 43 López Sousa et al., 2007; 32 MacLaren et al., 1995; 33 Miyao et al., 1984; 44 Moog et al., 2007b; 34 Moog et al., 2007a; 45 Narbay et al., 1996; 21 Nosti-Martinez et al., 1995; 22 Nowaczyk et al., 2000; 23 Parazzini et al., 1999; 46 Pascual-Castroviejo et al., 2005; 47 Rathoriya & Shrivastava, 2006; 24 Romiti et al., 1999; 48 Rubegni et al., 2003; 49 Sant'Anna et al., 1999 ; 25 Sanchez et al., 1981; 26 Savage et al., 1985; 50 Sofiatti et al., 2006; 51 Stieler et al., 2008; 27 Torrelo et al., 2005; 52 Valladares et al., 2007; 28 Walbaum et al., 1979; 53 Zielinska-Kazmierska et al., 2005

Table 3. Revised Diagnostic Criteria for ECCL

Eye

Major criteria

1. Choristoma, with or without associated anomalies

Minor criteria

1. Corneal and other anterior chamber anomalies
2. Ocular or eyelid coloboma
3. Calcification of globe

Skin

Major criteria

1. Proven nevus psiloliparis (NP)
2. Possible NP and ≥ 1 of minor criteria 2-5
3. ≥ 2 of minor criteria 2-5

Minor criteria

1. Possible NP
2. Patchy or streaky non-scarring alopecia (without fatty nevus)
3. Subcutaneous lipoma(s) in frontotemporal region
4. Focal skin aplasia/hypoplasia on scalp
5. Small nodular skin tags on eyelids or between outer canthus and tragus

CNS

Major criteria

1. Intracranial lipoma
2. Inraspinal lipoma
3. 2 of minor criteria

Minor criteria

1. Abnormal intracranial vessels, e.g. angioma, excessive vessels
2. Arachnoid cyst or other abnormality of meninges
3. Complete or partial atrophy of a hemisphere
4. Porencephalic cyst(s)
5. Asymmetrically dilated ventricles or hydrocephalus
6. Calcification (not basal ganglia)

Other

Major criteria

1. Jaw tumour (osteoma, odontoma or ossifying fibroma)
2. Multiple bone cysts
3. Aortic coarctation

Application of criteria to the diagnosis of ECCL

Definite case

1. 3 systems involved, major criteria in ≥ 2 , or
2. 3 systems involved, proven NP or possible NP + ≥ 1 of minor skin criteria 2-5
3. 2 systems involved with major criteria, one of which proven NP or possible NP + ≥ 1 of minor skin criteria 2-5

Probable case

1. 2 systems involved, major criteria in both
2. 2 systems involved, proven or possible NP