The following full text is a publisher's version.

For additional information about this publication click this link.
https://hdl.handle.net/2066/220456

Please be advised that this information was generated on 2020-09-03 and may be subject to change.
Oculoectodermal Syndrome – Encephalocraniocutaneous Lipomatosis Associated with NRAS Mutation

Renée J. H. RICHTERS1, Marieke M. B. SEYGER1, Kim A. P. MEEUWIS1, Tuula RINNE3, Astrid EIJKELENBOOM3 and Michèl A. WILLEMSEN4

Departments of 1Dermatology, 2Human Genetics, 3Pathology, and 4Pediatric Neurology, Amalia Children’s Hospital, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center, PO Box 9101, NL-6500 HB, Nijmegen, The Netherlands. E-mail: renee.richters@radboudumc.nl

Accepted Oct 18, 2019; Epub ahead of print Oct 21, 2019

Oculoectodermal syndrome (OES) and encephalocra-
niocutaneous lipomatosis (ECL) are rare overlapping
syndromes, caused by mutations of different genes in the
RAS-MAPK pathway. Symptoms defining these syn-
dromes are ocular abnormalities, such as dermoid cysts, and
ipsilateral malformations of the central nervous system.
We report here an exceptional case of a 3-day-old boy,
who presented with a congenital hairless area covered
with blister-like cutaneous lesions. Instead of known
variations of RAS-MAPK genes, HRAS, KRAS and
FGFR1, in the current case an NRAS variant was found.
This case is the first to describe an NRAS mutation as the
cause of these syndromes, and illustrates that genotypes
and phenotypes in the RAS-MAPK pathway strongly
overlap. The prominent bullae in this case have not been
described previously in oculoectodermal syndrome and
encephalocraniocutaneous lipomatosis.

CASE REPORT

A 3-day-old boy was referred to our outpatient clinic with a conge-
nital hairless area on the scalp covered with bullae. In addition to
these cutaneous lesions, he had had nodular lesions on the sciera
of the right eye since birth and hypoplasias. He was born to non-
consanguineous healthy parents, after an uncomplicated pregnancy
of 36 weeks and 6 days due to premature rupture of membranes,
and in good health. There was no family history of similar skin
lesions or autoimmune conditions. Physical examination revealed
a parieto-frontal yellow to erythematous atrophic hairless macule
on the right side of the scalp, with multiple nummular sharply
defined brown-to-violet firm bullae (Fig. 1). Overall, examina-
tion did not reveal any other cutaneous or mucosal abnormalities.
Microbial culture and PCR for herpes in the fluid of one of the
bullae, were negative.

Since there was no progression of the bullae and the child did
not seem to suffer from the cutaneous lesions, it was decided, in
agreement with the parents, to monitor the course of his condi-
tion under a diagnosis of congenital focal skin aplasia. Referral to
a paediatrician did not reveal any additional abnormalities. The
lesion on the right eye was diagnosed by an ophthalmologist as
a lipodermoid cyst. Re-examination after one month found that a
subcutaneous swelling was visible in the area of the bullae, whereas
the position and aspect of the bullae had not changed. Ultrasono-
graphy of the lesion and the underlying scalp revealed focal aplasia
of bone in the area of the increased subcutaneous swelling.

The patient was referred to the paediatric neurologist, who found
no clinical neurological abnormalities at that time, but requested
cerebral magnetic resonance imaging (MRI) due to suspicion of a
neurocutaneous syndrome. MRI revealed asymmetrical hemispheres
with a smaller right hemisphere volume, polymicrogyri of the
right parietal cortex, increased subarachnoid space, arachnoidal
cyctic configuration at the right temporal fossa, a choroid plexus
cyst in the right ventricle and small lacunar changes (Fig. 2). No
intracranial lipomatous abnormalities were found.

Genomic DNA was isolated from affected skin tissue, obtained
via a 4-mm skin punch biopsy, and from blood lymphocytes, in
order to identify gene variations causing ECL and OES. The
coding exons and intron-exon boundaries of the FGFR1 gene
(NM_023110) were sequenced either by Sanger or ion semicon-
ductor sequencing. Copy number variation in FGFR1 gene was
investigated by MLPA analysis (P133-C1 kit, MCR-Holland, The
Netherlands). In addition, single molecular Molecular Inversion
Probe (smMIP) based library preparation was performed followed
by NGS analysis on a NextSeq500 instrument (Illumina, San
Diego, CA, USA) including unique molecule identifiers (UMIs),
with an analytical sensitivity, as described by Eijkelenboom et al.
in 2016 (1). The panel included frequently mutated positions in
AKT1, BRAF, CTNNB1, CXXCR4, EGFR, ERBB2, EZH2, GNA11,
GNAQ, GNAS, H3F3A, H3F3B, HRAS, IDH1, IDH2, JAK2, KIT,
KRAS, MPL, MYD88, N Ras, PDGFRα, PIK3CA and SF3B1. No
unclassified or pathogenic variant, exon deletion or duplication was
identified in the FGFR1 gene in DNA isolated from lymphocytes

![Fig. 1. Photographs of the patient at the age of 3 days, showing: (a) erythematous atrophic hairless macules with multiple nummular sharply defined yellow-to-violet firm bullae; and (b) lipodermoid cyst of the right eye.](image)

![Fig. 2. Axial T2-weighted magnetic resonance images of the brain showing: (a) a large arachnoidal cyst at the right temporal fossa; and (b) a small volume of the right hemisphere, polymicrogyri of the right parietal cortex, and increased subarachnoidal spaces.](image)
DISCUSSION

OES and ECL are rare syndromes; only 20 and 50 cases of OES and ECL, respectively, have been reported (2, 3). These syndromes strongly overlap with respect to phenotype and genotype. Recently, OES has been considered a subtype of ECL (2, 4, 5). Ocular abnormalities, such as dermoid cysts, and ipsilateral malformations of the central nervous system contribute to the triad defining the syndromes. The diagnostic criteria for ECL were proposed by Hunter (6), including, amongst others, the following major criteria: (i) eye: ocular choristoma; (ii) skin: naevus psiloliparus (a mesodermal naevus of the scalp characterized by absence or paucity of hair and an excessive amount of fatty tissue); congenital craniofacial lipomas; multiple small craniofacial skin tags, skin aplasia or hypoplasia, possible findings of naevus psiloliparus with lipomas; (iii) brain: intracranial lipoma, intracranial calcification and arachnoid cysts. In OES, the eye and skin symptoms are also seen frequently, including epibulbar dermoids, focal aplastic skin defects and non-scarring alopecia of the scalp. A major difference is the lack of intracranial lipomatosis (5, 6). In the current case, intracranial lipomatosis could not be confirmed, suggesting the diagnosis of OES, which can be considered a subtype of ECL, according to recent literature (2, 6).

OES and ECL were found to be caused by mutations of different genes in the RAS-MAPK pathway (HRAS, KRAS and FGFR1), resulting in these overlapping phenotypes (2, 4, 5). Local involvement of the skin implies an underlying mosaicism. Mechanisms such as ectodermal dysgenesis and mosaicism are thought to be responsible for a mutated autosomal gene leading to mesenchymal tumours and vasculogenesis (7). In 2016, Bennett et al. (8), discovered mutations in FGFR1 in ECL, and therefore, this was the first analysis that we requested in order to find a mutation in this case. Later in 2016, ECL was linked to mutations in the RAS-MAPK pathway (8, 9). In 2015, Peacock et al. (3) also discovered mutations in the KRAS gene in 2 cases of OES, affecting p.Leu19Phe and p.Gly13Asp. Recently, these mutations have been shown in 4 other cases, affecting codon 146 of the KRAS gene (p.Ala146Val and p.Ala146Thr), confirming the role of the RAS-MAPK pathway (4, 10).

An NRAS variant in a mosaic pattern was found instead of a mutation in FGFR1 or KRAS. NRAS variants are known to play a role in congenital giant melanocytic naevi, Schimmelpenning-Feuerstein-Mims syndrome and Noonan syndrome (11). These variants have not been described previously in relation to OES/ECL. NRAS is also a RAS-MAPK gene and, therefore, it may not be surprising that mutations in NRAS also can lead to this phenotype. In 2017, Altmuller et al. (11) described phenotype and genotype spectra of NRAS variants, describing a case with ectodermal dysplasia and intracerebral arachnoid cyst and subcutaneous oedema. Next to this new variant, this is the first case in which blister-like cutaneous lesions have been described in a patient with OES/ECL. However, bullae have been described frequently in aplasia cutis in the context of syndromic or non-syndromic cases in general (12). NRAS mutations have not been described in relation to bullae. Given the convergent localization, however, we hypothesize that the bullae are part of OES/ECL, and therefore present a new clinical aspect of this uncommon disease.

In conclusion, this case is the first to describe an NRAS mutation as the cause of OES/ECL. It illustrates that genotypes and phenotypes in the RAS-MAPK pathway strongly overlap, and that in addition to HRAS and KRAS, NRAS mutations can also lead to OES/ECL.

REFERENCES