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Case Report

Nevus Sebaceous Syndrome: A Case Report and Literature Review of the Associated Neurological Complications

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- Schimmelpenning-Feuerstein-Mims syndrome

Abstract

The epidermal nevus syndromes (ENS) are a heterogeneous group of congenital anomalies characterized by epidermal or sebaceous nevi that are associated with extracutaneous manifestations that most often involve the central nervous system (CNS), ocular, and skeletal systems. We report a case of an 18-month-old female with widespread nevus sebaceous and brain and eye abnormalities.

INTRODUCTION

The incidence of epidermal nevi (EN) has been reported to range from 1 to 3 per 1000 live births affecting males and females equally [1]. The percentage of individuals with EN who have extra-cutaneous abnormalities (i.e. ENS) is not precisely known, and many estimates in the literature are overstated due to ascertainment biases. The most common extra-cutaneous associations involve the CNS, eye, and skeletal systems. The association of EN with CNS abnormalities has been recognized for many years. Schimmelpenning and subsequently Feuerstein & Mims [2], were among the first to describe the association. Solomon et al. [3], and Solomon & Esterly [1], provided the first comprehensive review of the associated neurologic (and other organ system) abnormalities. Since then, many reports and reviews have provided more detail and insight into the spectrum of the neurologic abnormalities associated with ENS. Estimates of the true incidence of CNS involvement in *all* patients with EN are probably as low as 5-15% but have been hampered by ascertainment bias, the paucity of accompanying histological data on the EN, and inconsistency in obtaining imaging studies documenting the CNS abnormalities. In addition, definitions of clinical findings vary considerably in different reports. In this report, we describe a neonate with a large nevus sebaceus (NS) on the head and face with accompanying neurologic and ophthalmologic manifestations and we review the recent neurologic literature to update the reader on current advances in our understanding of the associated neurological findings in this disorder.

CASE PRESENTATION

We report the case of an 18-month-old female delivered vaginally with a birth weight of 3020 g. Since birth, yellowish verrucous plaques were visible on the right parieto-temporo-cervical, thorax, and chin areas (Figure 1), with associated alopecia following Blaschko's lines (Figure 2). Extracutaneous abnormalities in the CNS, and eyes were present. The patient has an older sibling without skin issues and there is no family history of inherited diseases or skin problems.

The last prenatal ultrasound, conducted about four weeks before delivery revealed verrucous papules, megalocephaly, and cranial asymmetry, each of which were confirmed at birth. A newborn neurodevelopmental examination revealed hypotonia but by age 6 months, there was increased muscle tone, abnormal primitive reflexes as well as generalized seizures. In the following months, the patient showed delayed achievement of development milestones and increased muscle tone. At 18 months, the neurodevelopmental examination revealed contralateral (left side) muscle hypertonia, increased tendon reflexes, positive Babinski, and clonus in the ankle. The brain MRI showed focal cortical dysplasia ipsilateral of cutaneous findings.

The ophthalmological evaluation shows a right coloboma of

the upper eye, injection of the conjunctiva, left marginal corneal opacity, a whitish mass on the conjunctiva, and possibly an epibulbar dermoid (Figure 3). The parents of the child received care instructions and follow-up was scheduled but the family was lost to follow-up.

LITERATURE REVIEW AND DISCUSSION

Extracutaneous abnormalities are rare in isolated small NS and almost exclusively occur in the setting of extensive skin involvement. Since somatic mutations can occur at any point during embryogenesis, timing determines the relative size of the NS and the potential for extracutaneous manifestations. Mutations occurring later in embryogenesis will produce small, isolated NS with very low risk of other organ involvement, but earlier mutations are more likely to affect pluripotent cells that can differentiate into other tissue types (e.g. CNS).

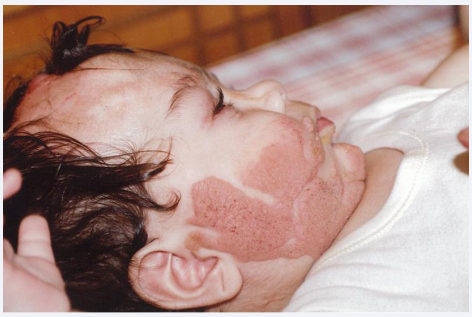


Figure 1 Verrucous plaques on the right mandible, cheek and chin.

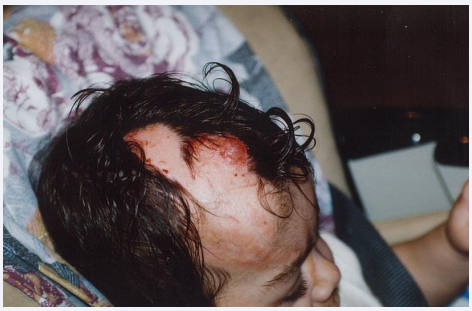


Figure 2 Alopecia along Blaschko's lines.

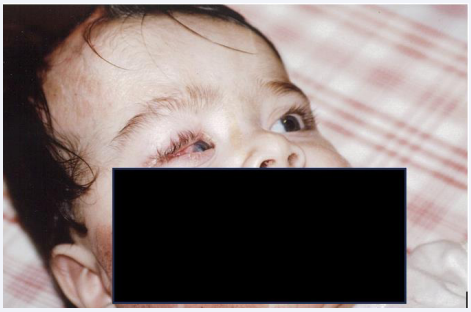


Figure 3 Right coloboma, conjunctival injection, conjunctival mass, left marginal corneal opacity, and possibly an epibulbar dermoid.

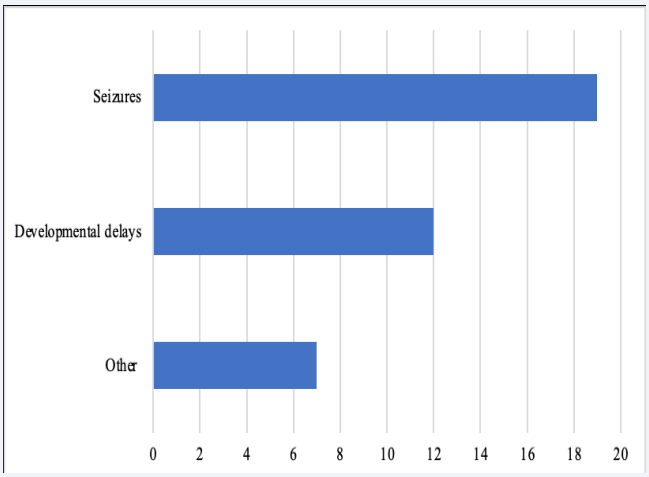
Several recent estimates suggest that less than 10% of NSS cases display neurological manifestations. Improved understanding of these cases is critical to accurate diagnosis and management for individuals with NSS who come for neurological consultations. However, literature on the neuropathologies of NSS is sparse and not readily accessible, given it is often buried in primarily dermatology case reports. The last comprehensive review of neurological manifestations associated with NSS was published in 2015 [4]. In this review, we will build on what is already known by examining the neurological aspects of NSS in case reports published since then, provide a summary of key dermatologic markers that could aid in a diagnosis of NSS, and explore the new developments on the genetic basis of NSS.

Relevant literature was found through PubMed and Google Scholar using the following search terms: "epidermal nevus syndrome", "nevus sebaceus syndrome", "nevus sebaceus syndrome", "Nevus sebaceus of Jadassohn" and "Schimmelpenning-Feuerstein-Mims". Case reports, literature reviews, and primary research articles were considered. The literature was reviewed for information on neurological manifestations of nevus sebaceus syndrome (NSS) as well as new updates on the genetic bases underlying NS specifically and mosaic neurocutaneous disorders in general. A total of 51 publications were selected from the literature review.

The neurological findings associated with NSS are frequently similar to keratinocytic epidermal nevi (KEN). As a result, distinguishing between the two conditions solely based on neurological symptoms is difficult. To address this, the current literature review includes cases involving NSS, *KEN*, and cases wherein a diagnosis of epidermal nevus syndrome (ENS) was made without further classification. Articles published between April 2015 and April 2023 were included. Non-English articles without a translation available directly from the publisher were excluded.

In terms of neurological findings, the most common symptoms included epilepsy and delayed motor, cognitive, and language functions. While MRI findings varied, hemimegaloencephaly and dysplasia were often present. Note that not all patients had MRIs taken. Additionally, not all patients who showed neurological symptoms had notable MRI findings, and vice versa. Graphical Figure 1a, 1b, 1c and Table 2 provide a comprehensive overview of neurological findings from the literature review. The right-hand columns in the tables show the number of cases for which that symptom or CT/MRI finding was present.

Cases of patients with conditions related to NSS, such as giant melanocytic congenital nevus (GCMN), rounded and velvety epidermal nevus (RAVEN), Garcia–Hafner–Happle syndrome i.e. FGFR3-ENS, and papular epidermal nevus with "skyline" basal cell layer (PENS) displayed similar neurological symptoms, with seizures and developmental delays (including cognitive delays) being common. Furthermore, a few patients with RAVEN and FGFR3-ENS also had autism spectrum disorder.



Graphical Figure 1a: Neurological Symptoms

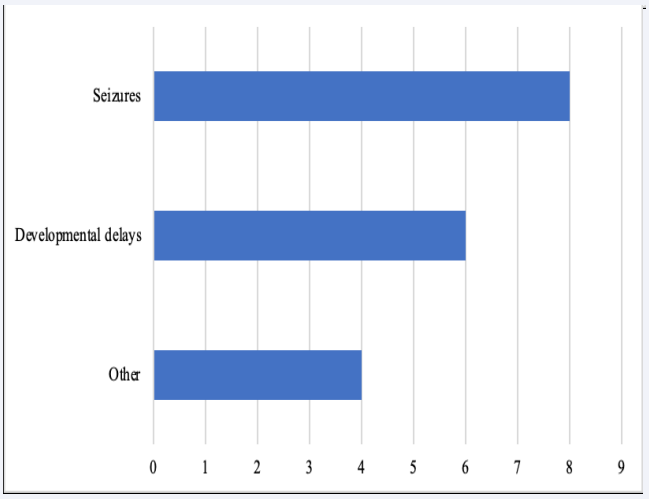
1a. Nevus Sebaceus Syndrome (NSS)

Seizures: Chacon-Camacho et al. [14], Chaves et al. [15], Chiang et al. [16], Deng at al. [17], Ezzi et al.[18], Gowdar et al. [19], Green et al. [20], Kuroda et al. [5], Lena et al. [21], Lihua et al. [22], Luo et al. [23], Miao et al. [24], Nagatsuma et al. [25], Ono et al. [26], Pan et al. [27], Pepi et al. [28], Salman et al. [29], Wang et al. [30].

Developmental Delays: Chaves et al. [15], Deng at al. [17], Ezzi et al. [18], Green et al.[20], Kapoor et al. [31], Lena et al. [21], Lihua et al. [22], Luo et al.[23], Nagatsuma et al. [25], Ono et al. [26], Pepi et al. [28], Salman et al. [29].

"Other" includes neurofibroma associated with the nevus [32], severe quadriplegia [17], plagiocephaly [33], asymmetry of spontaneous movements (no diagnosis provided) [28], hearing loss [34], hypoglossal palsy [34], and diffuse hypotonia [31].

Please note that in these cases, the authors did not provide a specific diagnosis beyond ENS.

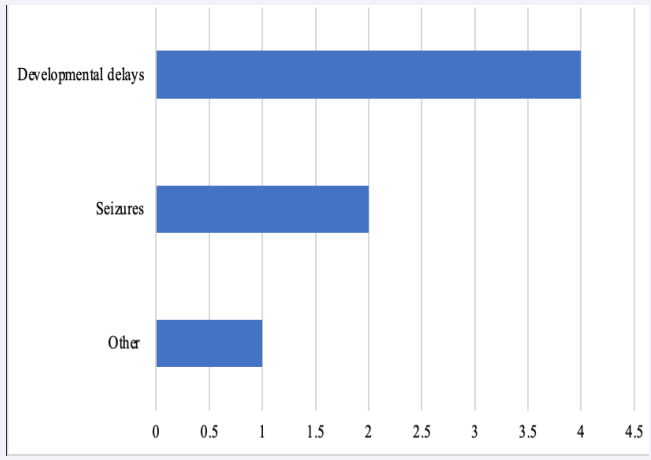


Graphical Figure 1b: Epidermal Nevus Syndrome (ENS) General

Seizures: De Vito et al. [60], Israni et al. [36], Ullah et al. [37].

Developmental Delays: De Vito et al. [60], Israni et al. [36], Ullah et al. [37].

"Other" includes nystagmus, right-sided weakness, headaches [35], significant scoliosis, and musculoskeletal pains [38]. The patient with scoliosis and musculoskeletal pains was also diagnosed with hypophosphatemia.



Graphical Figure 1c: Keratinocytic Epidermal Nevus Syndrome (KEN)

Seizures: Biçer et al. [39], Garg et al. [40].

Developmental Delays: Beyens et al.[8], Farschtschi et al. [41], Garg et al.[40].

"Other" includes a patient with cerebral palsy [40], and another patient with progressive transversal spinal cord syndrome as well as spasticity, paraparesis, pain, talipes equinovarus, positive Babinski reflex, and missing cremasteric and anal sphincter reflexes [41].

Cases of patients with conditions related to NSS, such as giant melanocytic congenital nevus (GCMN) [9], rounded and velvety epidermal nevus (RAVEN) [11], Garcia–Hafner–Happle syndrome i.e. FGFR3-ENS [7,42], and papular epidermal nevus with "skyline" basal cell layer (PENS) [43-45], displayed similar neurological symptoms, with seizures [9,44,7], and developmental delays (including cognitive delays) [11,45], being common. Furthermore, a few patients with RAVEN and FGFR3-ENS also had autism spectrum disorder [7,11].

Table 1: CT Findings

Asymmetry: asymmetry of lateral ventricle frontal horns: 2 [16,46] ,or ventriculomegaly:1 [14], interhemispheric asymmetry: 3 [14,18], one of which was diagnosed with hemimegaloencephaly [14].	6
Abnormal cranial structures: arachnoid cyst: 1[14], calcifications: 2 [16,22], dysplasia: 1[22]	4
Other	5
Cortical atrophy [14].	1
Enlarged Sylvian Valley [18]	1
Retinal coloboma [14].	1
Widened gap between brain and skull [30].	1
Polymicrogyria [14].	1

Table 2: Cranial MRI Findings.

Hemimegaloencephaly [5,35,19,36]	7
Abnormal cranial structures: cortical dysplasia: 7 **[9,25,29,35,36,37],** lipomas: 3 [25,29,35], cysts: 4 [16,31,21], medulloblastoma: 1 [9], Dysgyria: 4 [42,24, 47].	19
Atrophy of various structures – corpus callosum: 2 [42,22], cerebrum: 3][9,22], cerebellar: 1 [37].	6
Other	12
Widened peri cerebral spacing [18].	1
Cerebral infarction [17].	1
Cortical hamartomas [33,37].	2
Hippocampal asymmetry [15].	1
Displacement of the left occipital lobe across midline ("occipital sign") [36].	1
Extensive arteriopathy [18].	1
Incomplete operculization bilaterally [33]	1
Cortical malformations, either focal [33] or diffuse [28].	2
Periventricular leukomalacia (ischemic brain injury) [40].	1
Hippocampal sclerosis [22].	1

MUTATIONAL ANALYSIS

The mutations found in these conditions are only found in mosaic form. Germline mutations are almost always lethal and the vast majority of these mutations survive and manifest clinically only by occurring post-zygotically. Importantly, the earlier in embryogenesis they occur, the more widespread the nevus and the greater the chance (and more extensive and severe) of extracutaneous anomalies. Among patients diagnosed with NSS (which we consider identical to LNSS), HRAS mutations were the most common, including G13R [34,35,48-51], G12C [25], G12S [26], and G13V [23], as were KRAS mutations, specifically G12D [14,22,24,25,26,27,30], G12V [28], G12C [20,53], and A146T [31]. One NRAS mutation (Q61R) was found, marking the first causative NRAS mutation in NSS [5], as well as unique mutations such as in the PRKRIR gene (A1674T, R558S) for one patient, and a mutation in the RRP7A gene (C670T, R224W) in another [27]. Theiler et al. [6], examined cerebriform, papillomatous, and/or pedunculated sebaceous nevi from eight pediatric patients. In six of eight nevi, a mutation was found in the FGFR2 transmembrane domain mutation (either C382R or V395D) [6]. For a patient with FGFR3-ENS (Garcia–Hafner–Happle syndrome), two FGFR3 mutations were identified – R248C [7] and S249C [42].

For patients with KEN, primarily KRAS mutations were present: A146T [52], Q61R [44], G12D [41,54], as well as HRAS G12C and Q61L mutations [55]. For one KEN patient, a maternally inherited duplication in the first two exons of the HUWE1 gene was found; this gene is known to be associated with neurodevelopmental and intellectual disability [52].

This literature review also captured a few conditions that are less related to NSS: A patient with giant melanocytic congenital nevi (GMCN) had an NRAS (Q61R) mutation [9], a patient with Costello Syndrome had an HRAS (G12S) mutation [10], a patient with RAVEN had a mutation in the FGFR2 gene (C382R) [11], and finally, a patient diagnosed with a verrucous epidermal nevus and hystrix-like ichthyosis was found to have mutations in the GJB2 gene, which encodes a member of the gap junction protein family [12]. Two patients were diagnosed with ENS, with no further specification of subtype. These patients both had HRAS mutations, either G12S [56], or G13R [57].

Kim et al. [58], showed that the introduction of the KRAS G12V mutation in the developing mouse subcortex recapitulates several of the major pathological manifestations of LNSS and that several of these manifestations such as delayed neuronal maturation are reversed by the clearance of KRAS G12V. Thus, they provide insights into the ability of Ras mutations to lead to disorganized cortical neuronal development (similar to that seen in the skin) and interestingly some promise of reversibility at least in animal models [59].

Overall, this study describes the case of an 18-month-old female with nevus sebaceus syndrome. Utilizing a comprehensive literature review of relevant publications since 2015, we describe neurological symptoms associated with NSS, general ENS, and conditions closely related to NSS, such as KEN. We also characterize neurological imaging results, where available. Finally, we summarize a detailed analysis of mutations associated with ENS. Together, this information may provide valuable data for those managing patients with ENS.

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