Case Report

Neuroimaging manifestations of epidermal nevus syndrome

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Abstract: Epidermal nevus syndrome (ENS) represents a diverse group of rare neurocutaneous diseases associated with the presence of characteristic epidermal nevi (EN) in the skin and extracutaneous manifestations in the eyes, skeletal, urogenital and central nervous systems. We present a case series of 7 children with ENS, with specific attention to the neuroradiological characteristics of this entity.

Keywords: Central nervous system diseases; hemimegalencephaly (HME); linear sebaceous nevus syndrome

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Introduction

Epidermal nevus syndrome (ENS) is a term used to represent a diverse group of neurocutaneous diseases in which one of the subtypes of epidermal nevi (EN) are found in association with extracutaneous abnormalities involving the eyes, nervous, skeletal, and urogenital systems (1). Most EN are present at birth and typically follow the lines of Blaschko (2). Blaschko's lines refer to the S-shaped or V-shaped whorled, streaked, and linear patterns that are believed to represent the dorsoventral migratory pathways of the neuroectoderm during embryogenesis (2). The incidence of EN has been reported to range from 1 to 3 per 1,000 live births, without gender predominance (2,3). Numerous phenotypes with different clinical appearances and histopathological features have been described (4), such as the nevus sebaceous syndrome (NS), nevus comedonicus syndrome (NC), phakomatosis pigmentokeratotica (PPK), proteus syndrome, and congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome (5). In terms of CNS abnormalities however, hemimegalencephaly (HME) is the most striking finding, typically found on the side of the skin lesion, associated often with polymicrogyria (4,6). Other neuroimaging findings can be grey matter heterotopia, atrophy with dystrophic calcification and hamartomas (7,8). Cerebellar involvement has also been described. Vascular abnormalities are rare, including vessel dysplasia and infarction (9). The molecular basis of ENS spectrum is unclear. The syndrome has been observed sporadically in the relatives of affected patients. It has been hypothesized that it is a form of mosaicism of a lethal autosomal dominant gene (5,10). Recent reports of somatic mosaicism in the pathogenesis of ENS have been reported, along with the identification of *HRAS* and *KRAS* mutations (11,12).

Case presentation

Case 1

A 7-year-old girl presented with new-onset of generalized seizures and developmental delay in multiple domains. Physical examination revealed an epidermal nevus on the left trunk. Ophthalmological assessment showed bilateral optic nerve colobomata and corneal opacification. Brain MRI demonstrated two small lipomas on the dorsal surface of the cervicomedullary junction (*Figure 1A*). There was also moderate generalised cerebral atrophy (*Figure 1B*) with

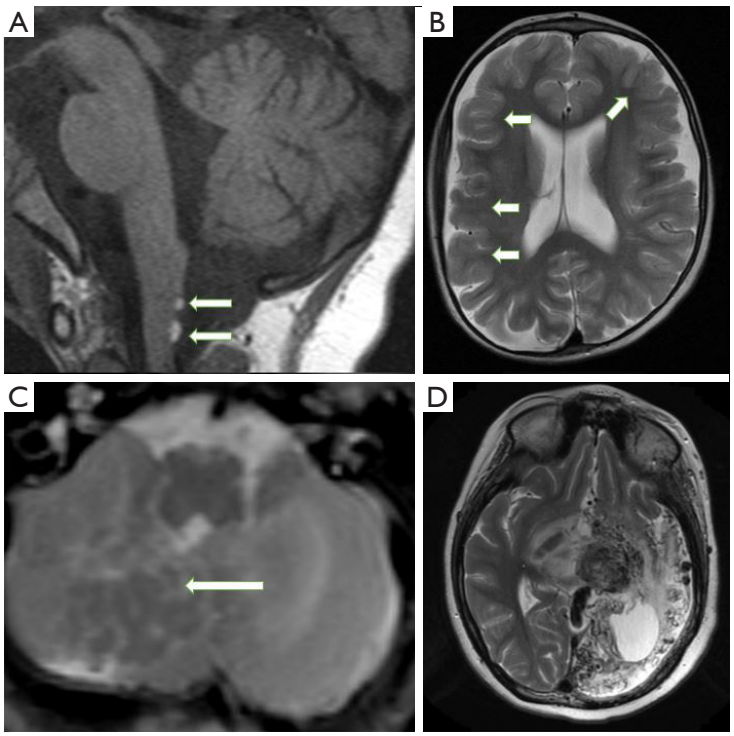

Figure 1 MRI scans showing cerebral and cerebellar abnormalities. (A) Sagittal T1-WI showing two dorsal cervico-medullary lipomas. (B) Axial T2-WI showing generalized brain atrophy with some areas of cortical dysplasia (arrows). (C) Axial T2-WI showing right cerebellar grey matter heterotopia (arrow). (D) Axial T2-WI showing left hemispheric proliferative arteriopathy.

mild prominence of the subarachnoid spaces overlying both hemispheres and inferior cerebellar vermian dysplasia.

Case 2

A female infant presenting with right-sided seizures at week 1 of life, with evidence of an epidermal nevus of the neck and right cheek noticed at 6 months of age. Right hemifacial hypertrophy, prominent right eye with associated exotropia and congenital nystagmus were noted on examination. Brain MRI at 1 month of age showed right cerebral HME with extensive areas of cortical dysplasia and associated neuronal migrational abnormality within the cerebellum, consistent with heterotopic grey matter (*Figure 1C*).

Case 3

A 3-day-old boy with right facial hypertrophy, right epidermal nevus, right ocular enlargement, nystagmus and developmental delay presented with medical refractory right-sided seizures. CT and MRI scan performed at day 9 of life showed an extensive right cerebral and cerebellar HME. He underwent functional hemispherectomy at the age of 12 months.

Case 4

A 7-year-old girl was diagnosed with a large left neck and cheek epidermal nevus. Left cerebral arterio-venous malformation was diagnosed when she presented with right sided weakness and refractory seizures. She underwent multiple embolizations. Historical images were not available but CT scan and MRI scan at age 18 showed a left-sided extensive proliferative arteriopathy with associated brain atrophy (*Figure 1D*).

Case 5

An 8-year-old boy presenting with vomiting and headache. He was noted to have a right facial nevus. Brain MRI revealed a large medulloblastoma in the posterior right cerebellar hemisphere which was resected in 2015 (*Figure 2A*). He had

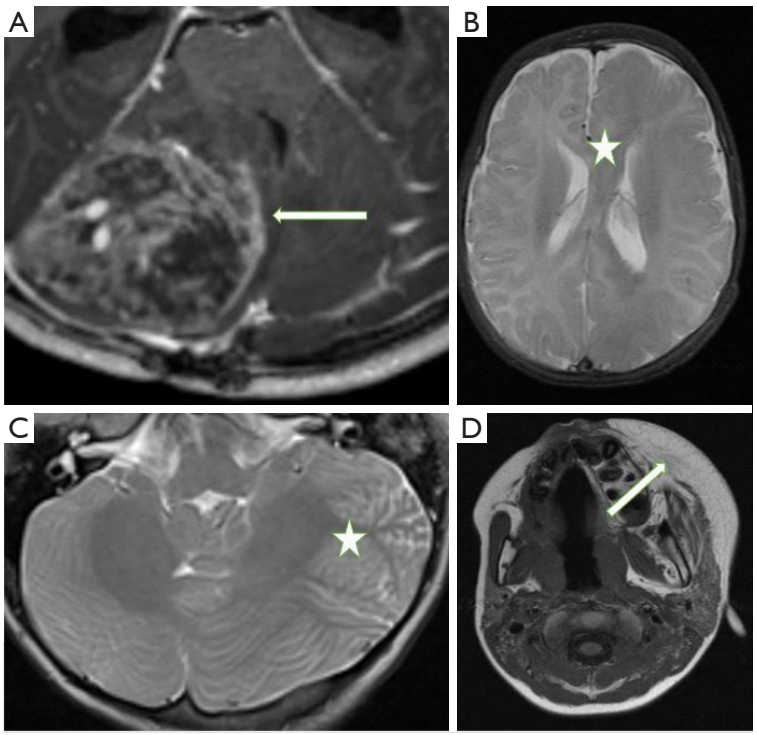

Figure 2 MRI scans showing supra- and infratentorial abnormalities. (A) Axial T1-WI after contrast administration showing a right cerebellar hemispheric medulloblastoma. (B) Axial T2-WI showing left HME involving the corpus callosum (star); (C) Axial T2-WI showing left cerebellar hemimegalencephaly (HME) with associated cortical dysplasia (star); (D) Axial T1-WI showing left facial lipomatous hypertrophy.

a large local recurrence 3 years later.

Case 6

An 8-year-old boy with left facial hypertrophy and ipsilateral neck and trunk nevus presented with new onset left-sided seizures and developmental delay. Brain MRI showed a left cerebral and cerebellar hemispheric (*Figure 2B*) HME with extensive cortical dysplasia within both structures (*Figure 2C*).

Case 7

A 15-month-old boy presenting with new-onset focal left frontal epilepsy and developmental delay. Physical examination showed a left facial nevus. Brain MRI revealed an extensive left cerebral HME (*Figure 2D*).

Discussion

ENS is not one disease, but rather a heterogeneous and diverse cluster of different disorders which have been categorized together (10). Several specific syndromes with overlapping features have been described, namely, the NS syndrome, Proteus syndrome, PPK (coexistence of nevus sebaceous with melanocytic nevi) and Keratinocytic ENS (10-14). These have been summarized in *Table 1*.

The cutaneous features of ENS depend on the predominant cell type involved histologically, the degree of cellular differentiation, the body site involved, and the age of the patient. EN typically follow several well recognized patterns of cutaneous mosaicism, typically "the lines of Blaschko" (2). Various methods of classifying EN have been proposed over the years. The concept that nevi may show differentiation towards various skin structures and glands, comprising of pilosebaceous, apocrine, eccrine glands and keratinocytes, has been the basis of most clinical classifications to date (5,15). The two main subtypes are Nevus sebaceus (with excessive sebaceous glands components) and Keratinocytic EN (lesions without any adnexal components).

In terms of the genetic basis of ENS, the published evidence suggests that the clinical expression of ENS is based on genomic mosaicisms (16). The primary genes

Table 1 Classification of epidermal nevus syndrome

Syndrome	Type of epidermal nevus	Salient clinical features	Genetics
Nevus Sebaceous syndrome	Nevus Sebaceous	Nevus Sebaceous and epibulbar lipodermoid	KRAS
Phakomatosis Pigmentokeratotica	Nevus Sebaceus	Additional presence of nevus spilus papulosus, arranged in a checkerboard pattern	HRAS
Nevus Comedonicus syndrome	Nevus Comedonicus	Ipsilateral cataract and skeletal anomalies	FGFR2
Becker Nevus syndrome	Becker Nevus	Breast hypoplasia in females, hypertrichosis in males, no CNS involvement	Undefined
Proteus syndrome	Keratinocytic Nevus	Cerebriform connective tissue nevi of palms or soles; asymmetric macrodactyly	AKT
CHILD syndrome	CHILD Nevus	Lateralized, inflammatory skin lesions; ptychotropism; ipsilateral limb defects	NSDHL mutations
Keratinocytic Nevus syndrome	Keratinocytic Nevus	Presence of keratinocytic nevus of the common type; absence of lesions of disproportionate overgrowth	FGFR3

FGFR, fibroblast growth factor receptor; AKT, protein kinase B; NSDHL, NAD (P) dependent steroid dehydrogenase-like.

thought to be responsible for ENS are the ones involved in the Ras/MAPK signaling pathways; hence the term mosaic RASopathies is commonly used (11). The genes involved in the pathway include KRAS, HRAS, NRAS and FGFR1 (11,17,18). FGFR2 and FGFR3 mutations have also been reported to be involved in some cases (11,19).

Sebaceous Nevi are mostly located on the scalp or face, although they can be more widespread. They have a salmon to yellow color and a characteristic smooth waxy surface and can be complicated by eczematous reactions (14). Keratinocytic EN (KN) are another type of EN typically found on the trunk and extremities. They appear as linear or whorled skin-colored to pink or slightly hyperpigmented plaques that may be unilateral or bilateral.

Central nervous system involvement has been noted to be the most commonly described systemic association with ENS, presenting with a constellation of signs and symptoms ranging from headaches, epilepsy, focal motor deficits and developmental delay (20). Ophthalmological findings described include epibulbar lipodermoid, coloboma, corneal opacities and defects of the optic nerves, while associated skeletal abnormalities are craniofacial defects, frontal bossing, kyphoscoliosis, hip dislocation and limb deformities (21,22).

Spanning the last 20 years, some cases of ENS have been published describing their neuroimaging manifestations, as summarized in *Table 2*. Our search strategy on PubMed, developed in consultation with a librarian with expertise in health research and systematic reviews, included terms related to ENS HME (in studies published from 1995). A broad approach was taken through the inclusion of all possible synonyms and abbreviations for the terms of interest, and controlled vocabulary/ subject headings (including MeSH, EmTree).

HME

HME is the most common structural brain abnormality encountered in the different subsets of ENS. As a corollary, ENS is the most common neurocutaneous disorder associated with HME (28). The distinctive triad of hemifacial EN, ipsilateral HME, and lipoma was first described by Gross and Uiberrak in 1955, who introduced the term "hemimegalencephaly." Pavone and colleagues also reported HME in 17 out of 60 patients with ENS, their study being a review of the literature and based on pathology or CT studies (28). Menascu *et al.* (25) described MRI abnormalities in 3 patients with ENS showing HME, polymicrogyria and cortical heterotopia while Pavlidis *et al.* (26) reported a boy with right 'total' HME, with increased volume of both cerebellar and cerebral right hemisphere.

In our series, HME was found in 4 patients out of 7,

Table 2 Literature review

Authors	No. of patients	Neuroimaging findings
Dodge *et al.* 1995 (23)	1	Left HME, pachygyria, absence of the corpus callosum, and type A Dandy-Walker malformation
Booth *et al.* 2002 (9)	2	Cervicomedullary subpial lipomas, cerebral cortex dysplasias
Abdelhalim *et al*. 2003 (6)	1	Asymmetric bilateral hemispheric enlargement and diffuse pachygyria. The right cerebellar hemisphere was large, with disorganized cerebellar folia
Neumann *et al.* 2003 (7)	1	Asymmetry with cortical hypoplasia on the left side and giant cystic enlargement of Virchow-Robin spaces.
Zhang *et al.* 2003 (4)	3	Hemimegalencephaly, heterotopia, calcifications and gyral fusions
Canygit *et al.* 2006 (24)	1	Intracranial left orbital and left cerebellopontine angle cistern lipomas, thinning of the left internal carotid artery, left cerebral HME
Menascu *et al*. 2008 (25)	2	Hemimegalencephaly, heterotopia, polymicrogyria
Pavlidis *et al*. 2011 (26)	1	Right 'total' HME, with increased volume of both cerebellar and cerebral right hemisphere, PMG
Okumura *et al*. 2012 (8)	1	Medulloblastoma associated with supratentorial cortical dysplasias, a dysmorphic enlarged midbrain and a small cerebellum with dysplastic folias
Ullah *et al.* 2016 (27)	1	Cortical dysplasia and multiple hamartomas in the medial temporal lobe, thalamus, and periventricular region on right side and cerebellar atrophy with Dandy-Walker variant

HME, hemimegalencephaly; PMG, polymicrogyria.

mostly right-sided. 2 of these patients showed both cerebral and cerebellar involvement. Furthermore, HME was always ipsilateral to the epidermal nevus.

Cerebellar involvement

Dodge *et al.* showed severe hypoplasia of the cerebellum with upward rotation of the vermis and a large retrocerebellar cyst in a 6-month old girl with infantile spasms (23). Also, Ullah *et al.* (27) reported cerebellar atrophy and cerebral cortical dysplasia in a 25-year-old girl. Abdelhalim *et al.* (6) reported an infant with ENS characterized by enlargement of both cerebral hemispheres, malformed basal ganglia, and unilateral enlargement of cerebellar hemisphere with disorganized folia.

Infratentorial anomalies were shown in 5 patients of our series, represented by HME, atrophy (unilateral and bilateral) and cerebellar heterotopia.

Lipomas

Intracranial and intraspinal lipomas represent rare manifestations of ENS; 2 patients from Booth *et al.* (9) showed the presence of subpial lipomas dorsal to the cervicomedullary junction, in association with very subtle dysplasias involving the cerebral cortex ipsilateral to the nevi. Left orbital and left cerebellopontine angle cistern lipomas were present in the series from Canyigit *et al.* (24).

We found 2 dorsal cervicomedullary lipomas in 1 patient, in association with cerebral and cerebellar atrophy.

Neoplasms

Bourdeaut *et al.* reported an oncogenic KRAS mutation in a patient with ENS associated with rhabdomyosarcoma (12) while Okumura *et al.* (8) showed a 51-day-old boy with neonatal medulloblastoma associated with cerebral and cerebellar cortical dysplasia. A right lateral medulloblastoma was present in 1 patient from our series, along with an ipsilateral nevus.

Vascular abnormalities

Juan *et al.* (29) revealed multiple sites of intra-thoracic and abdominal arterial stenoses and aneurysm formations

in association with ENS in one patient, while Canyigit *et al.* (24) reported a 27-month-old boy with thinning of the left internal carotid artery (ICA) with occlusion at the T-junction.

We had one case with the presence of a large hemispheric arteriovenous malformation that was embolized on multiple occasions.

Differential diagnosis

ENS overlaps with HME spectrum of disorders, some entities within both these two groups being caused by similar mutations in the mTOR pathway. As such, HME with the co-existence of an epidermal nevus is very specific for ENS.

Further, within the neurocutaneous metameric disorders, Sturge-Weber syndrome (SWS), PHACES, MCAP (Megalencephaly-Capillary malformation), Parry-Romberg Syndrome (PRS) and encephalocraniocutaneous lipomatosis (ECCL) may all present as potential differentials, but associated CNS manifestations like a pial angioma (SWS) or characteristic segmental hemangiomas with posterior fossa malformations, ocular and cerebral arteries anomalies (PHACES), or hemifacial atrophy with both brain parenchyma anomalies (PRS), or presence of craniofacial lipomas with regional brain malformation (ECCL) (30) help differentiate these entities from ENS.

ENS is a rare spectrum of neurocutaneous disorders, all characterized by the presence of different types of EN with associated extracutaneous manifestations. CNS symptoms are common and ocular, skeletal and urogenital findings can be associated. Intracranial involvement is best evaluated with MR imaging and neuroimaging findings range widely, with the most common finding being HME. Rarer findings include intracranial/intraspinal lipomas, vascular anomalies and neoplasms.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/qims-20-634). Dr. KM serves as an unpaid Associate Editor of *Quantitative Imaging in Medicine and Surgery*. The other authors have no conflicts of interest to declare.

Ethical Statement: Written informed consent was obtained from the patients for publication of this study and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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