CASE REPORT

An Egyptian boy with Haberland syndrome: Case report with observations on the histopathology

Rania Alakad, MSc,a Ahmad Nofal, MD,a Magda Assaf, MD,b Khaled Gharib, MD,a Waleed Albalat, MD,a Engy Tantawy, MD,c and Waleed Ashour, MDd

Sharqia, Egypt

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INTRODUCTION

Haberland syndrome is characterized by diverse malformations affecting the ecto-mesodermal tissues (the central nervous system, the eye, and the skin). The most prominent anomalies include a hairless fatty tissue nevus of the scalp (nevus psiloliparus) and ocular choristomas.1 In addition, several central nervous system (CNS) anomalies have been described, including cranial and spinal lipomas, partial or complete hemisphere atrophy, and intracranial cysts that can lead eventually to mental retardation and/or seizures.2 We present a case of Haberland syndrome that met the revised diagnostic criteria proposed by Moog in 20092 and can be considered a definite case of Haberland syndrome despite the absence of a fatty nevus. In addition, we demonstrate that the histopathologic findings of vascular hyperplasia are a prominent feature of all involved sites.

CASE REPORT

A 13-year-old boy was referred to our outpatient clinic with a large patch of nonscarring alopecia on the left fronto-parietal scalp dating since birth (Fig 1). History of epileptic fits along with weakness confined to the right side of his body was reported by the parents at the age of 4 years. There was neither a history of parental consanguinity or birth trauma nor a family history of developmental problems. General examination findings were normal except for a slight increase in the head circumference, which was above normal for age at 23.6 inches (average 20.5 – 22 inches). Mental development was otherwise normal. On dermatologic examination, multiple skin-colored skin papules resembling skin tags were noticed on the left upper eyelid and eyebrow (Fig 2, A). Small depressed atrophic macules were also seen on the left side of the forehead and above the left eyebrow. Ophthalmologic evaluation of the left eye found conjunctival congestion, hypertrophy of the bulbar conjunctiva, and a yellowish red conjunctival nodule consistent with limbal dermoid (Fig 2, B). Fundus examination of both eyes was normal.

Neurologic examination found spasticity (hypertonia and hyperreflexia) at the right side indicating upper motor neuron lesion. Computed tomography scan of the brain showed a left parieto-occipital

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porencephalic cyst, left temporal arachnoid cyst, and left parietal schizencephaly encroaching the left cerebral hemisphere along with cerebral calcifications (Fig 3). Electrocardiography, echocardiography, abdominal ultrasonography, magnetic resonance imaging of spine, and x-ray of the jaw were unremarkable.

Biopsy specimens were taken from the 3 involved sites: the hairless patch, the lid papules, and the hypertrophied conjunctiva. Histopathologic examination of the involved scalp found absent hair follicles and fibrovascular stroma with remnants of degenerated muscle fibers (Fig 4). Biopsy of the lid papules found hamartomatous mass of fibrovascular stroma resembling an angiofibroma (Fig 5), while the conjunctival biopsy found fat deposition of mature adipocytes (Fig 6). Minimal inflammatory infiltrate in the form of lymphocytes together with small collections of mast cells were evident at higher magnification in both skin and conjunctival lesions. In addition, vascular hyperplasia of variable-sized blood vessels was prominent in all biopsy specimens. Based on the existing clinical, pathologic, and imaging findings, a diagnosis of Haberland syndrome was made.

**DISCUSSION**

Haberland syndrome is characterized by cutaneous malformations, usually on one side of the body, with ipsilateral CNS and ocular abnormalities and occasionally visceral lipomas. The malformations tend to be unilateral, although bilateral involvement has been described. In 2006, Hunter had reported a large series of Haberland patients and accordingly proposed diagnostic criteria, which had
been later revised by Moog\textsuperscript{2} in 2009. According to the revised diagnostic criteria, our patient fulfilled the criteria for a definite case of Haberland syndrome (3 systems involved, major criteria in $\geq 2$).

Other disorders share similar features with Haberland syndrome including Proteus syndrome, oculocerebrocutaneous syndrome (Delleman-Oorthuys syndrome), nevus sebaceous syndrome, Goldenhar syndrome, epidermal nevus syndrome, and oculoectodermal syndrome. Haberland syndrome was previously viewed as a localized form of Proteus syndrome; however, many features can clearly distinguish between both entities (Table I).\textsuperscript{2}

The exact pathogenesis is not yet fully elucidated with the theory of cephalic neural crest, and anterior neural tube dysgenesis is the most widely accepted one. Most of the tissues affected in Haberland syndrome are neural crest derivatives, such as the meninges and cranial vessels (presented as cranial and spinal lipomas beside meningeal and vascular defects), dermis and hypodermis of the face and neck (nevus psiloliparus, scarring and non-scarring alopecia, and subcutaneous lipomas), and head mesenchyme (ocular choristomas). Hence, Haberland syndrome is a mesenchymal disorder, and all CNS anomalies are caused by a mesenchymal
defect affecting the tissues surrounding the brain or the vessels.2

Haberland syndrome is considered a mosaic condition with sporadic nature because of the patchy pattern of the developmental anomalies, especially the cutaneous ones. Mosaic heterozygous or biallelic mutations have been suggested but not confirmed so far.3

The histopathology of the scalp in our case showed features of nonscarring alopecia (absent hair follicles without fatty nevus). The lid papules demonstrated hamartomas formed of disorganized elements of fibrous and vascular tissue resembling angiofibromas. The skin-colored eyelid tags in Haberland syndrome are reported to represent lipomas, fibromas, fibrolipomas, angiofibromas, and connective tissue nevi or hamartomatous tissue formed of cartilage, fat, and connective tissue.4 Despite the absence of fat deposits in our cutaneous lesions, the conjunctival biopsy found lipomatous infiltrate. In addition, small collections of mast cells were interestingly found in the dermal inflammatory infiltrate in both scalp and eyelid lesions. Mast cell infiltrate has been reported in the lesions of Haberland syndrome; however, its significance in the pathogenesis of the syndrome is not yet explored.5,6

Vascular hyperplasia and angiogenesis were the histopathologic hallmarks of the 3 involved sites in our case. Large thick-walled blood vessels together with newly formed ones were noticed. We propose that this finding is consistent with the etiologic hypothesis of a mutated autosomal gene responsible for the vasculogenesis and the development of multiple mesenchymal tumors.2 To our knowledge, vascular hyperplasia has been reported once before in Haberland syndrome by Sanchez et al,6 who noticed capillary dilatation and hyperplasia in a biopsy specimen taken from a papule on the temple. On the contrary, we found prominent vascular hyperplasia in both the cutaneous (scalp and lid papule) and conjunctival lesions. Moog et al3 reported the presence of intracranial vascular defects in the form of abnormal or excessive vessels causing leptomeningeal angiomatosis, but no similar vascular changes have been observed in the skin and eye lesions.

It is noteworthy that fatty nevus was found underlying the scalp alopecia in 81% of cases,2 so its absence should not exclude the definite diagnosis of Haberland syndrome as was the case in our patient. Being a constant feature in all reported cases, we suggest that alopecia (whether scarring or nonscarring) is a more reliable major criterion than fatty nevi in the diagnosis of Haberland syndrome. In addition, the variable existence of fat deposits (subcutaneous, conjunctival, or intracranial) in the reported cases4,7 reinforces the need to revise the encephalocraniocutaneous lipomatosis nomenclature and to stick to the nonconfusing term of Haberland syndrome.

Here we described the first, to our knowledge, Egyptian case of Haberland syndrome presenting with the typical clinical and imaging features and showing unique histopathologic findings in the form of prominent vascular hyperplasia in both cutaneous and conjunctival lesions.

Table I. Comparison of Haberland syndrome and Proteus syndrome

| Developmental anomalies | Haberland syndrome | Proteus syndrome |
|-------------------------|--------------------|-----------------|
| A cerebriform connective tissue nevus | Usually present at birth and nonprogressive | Not present |
| Skeletal anomalies | Nonprogressive and underlie areas of alopecia or fatty tissue nevus. | Hyperostoses of the skull are disproportionate, progressive with distorting overgrowth |
| Dysregulation of adipose tissue | Intracranial and spinal lipomas | Lipomas |
| | Fatty tissue nevus on the scalp | Lipohypoplasia |
| | Subcutaneous fatty masses | Fatty overgrowth |
| Vascular anomalies | Intracerebral vessel anomalies are common | Uncommon feature |
| Ocular anomalies (Choriostomas) | Frequent | Less common |

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