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Clinical Observations

The Microcephaly-Capillary Malformation Syndrome in Two Brothers With Novel Clinical Features

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ABSTRACT

BACKGROUND: Microcephaly-capillary malformation syndrome is a newly described neurocutaneous entity that is characterized by congenital and progressive microcephaly, intractable epilepsy, profound developmental delay, multiple small capillary malformations on the skin, and poor somatic growth. Recently, mutations in the *STAMBP* gene have been identified as causative in the pathogenesis of this syndrome. **PATIENTS:** We describe two brothers (ages 7 and 12 years) from consanguineous parents of Saudi ancestry. Along with the established main clinical features of this syndrome, these boys exhibited certain novel and distinctive phenotypic features (congenital hypothyroidism and autistic-like behavior with intermittent repetitive hand-flapping movements). Genetic studies revealed the presence of homozygous pathogenic *STAMPB* mutation. **CONCLUSION:** This report presents the longest follow-up of patients with microcephaly-capillary syndrome so far reported and emphasize the syndrome's phenotype variability.

Keywords: microcephaly-capillary malformation syndrome, epilepsy, *STAMBP* mutation, global developmental delay

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Introduction

"Microcephaly-capillary (MIC-CAP) malformation syndrome" (ORPHA number, 294016) is a newly described entity characterized by congenital and progressive microcephaly, intractable epilepsy, profound developmental delay, multiple small capillary malformations on the skin, and poor somatic growth.[1-3] This novel syndrome was initially hypothesized to be caused by one or more genes involved in vasculogenesis and neuronal and growth regulation.[3] Recently, by using entire exome sequencing in a group of affected patients, the mutation in the *STAMBP* (STAM: signal transducing protein involved in intracellular signal transduction mediated by cytokines and growth factors, BP: binding protein) gene was found. This gene, mapped on chromosomal locus 2p13.1, encodes the deubiquitinating isopeptidase-associated molecule with the SH3 domain of *STAM* that plays a key role in cell surface receptor-mediated endocytosis and sorting.[4]

To date, 10 patients with the clinical features of MIC-CAP syndrome have been reported, the oldest being 5 years 4 months old.[1-5] We describe slightly different clinical phenotypes and a longer follow-up of two brothers (ages 7 and 12 years) from consanguineous parents of Saudi ancestry and currently living in Kuwait.

Patient Descriptions

Patient 1

This boy, 12 years old, is the first child of first degree healthy consanguineous parents. The perinatal history is unremarkable; he was delivered at term (39 gestational weeks) via normal spontaneous vaginal delivery with Apgar scores of 8 and 9 at 1 and 5 min, respectively. The birth weight was 2.6 kg (third percentile), birth length was unknown, and birth occipitofrontal circumference (OFC) was 31 cm (2 cm below third percentile).

At birth he had numerous cutaneous macular changes, recognized to be capillary malformations. He was also observed to have ulcerated areas

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in the scalp, characterized by the dermatologist as aplasia cutis congenita. There were also noteworthy dysmorphic facial features, including hypertelorism, long philtrum, low-set ears, as well as hypoplastic distal phalanges and toe nails. He had micropenis and undescended testes.

His first seizures, preceded by fever, began at age 7 months, and they were soon followed by recurrent afebrile and febrile seizures, being either focal or secondary generalized. He had an episode of status epilepticus. Seizures were often refractory to multiple antiepileptic medications and required frequent hospitalizations. Initially, he was treated with sodium valproate and later on with carbamazepine, levetiracetam, phenytoin, and topiramate in different combinations. During the last few years, seizure control has been remarkably improved, and he has been seizure free for almost 3 years. His current medications include valproic acid and topiramate.

At age 18 months, it was evident that he had raised thyroid stimulating hormone, and consequently, he was initiated on L-thyroxin supplementation, which he has been continuing since.

His somatic growth was marked by slow growth. Throughout the entire period of developmental follow-up, his weight and height along with head circumference remained around or under the third percentile. However, there was no progressive decline in head growth velocity.

His behavior was mostly stable, with prominent sleep problems requiring frequent administration of chloral hydrate or melatonin.

On the last recorded physical examination at 12 years, his weight was 24 kg (2 kg below third percentile), length was 130 cm (third percentile), and OFC was 49.5 cm (1 cm below third percentile). Numerous capillary malformations involving the trunk and extremities were of different size, a shape and hyperpigmented appearance (Fig 1A,B). There was a discrete whirling hair pattern along with a scar-like aplastic skin over the central scalp and high rounded shape of the anterior hairline (Fig 2A,C). His feet had hypoplastic distal phalanges with dystrophic nails (Fig 2C).

Neurological examination revealed a globally impaired child, autistic-like behavior, and intermittent choreiform movements of the head and arms in addition to repetitive hand-flapping movements accompanied by vocalization. Neither targeted visual tracking nor verbal communications were present. There were convergent squint and poor facial expression. Muscle tone was mildly increased with 2+ deep tendon reflexes in the upper and lower extremities. He could make a few steps unsupported out of his wheelchair.

His karyotype analysis, blood amino acids analysis, urine organic acids, very long chain fatty acids, and toxoplasmosis, rubella, cytomegalovirus, herpes simplex (TORCH) titers were within normal limits. A fundoscopic examination revealed mild bilateral optic nerve hypoplasia. An echocardiogram and abdominal ultrasound imaging were normal. Brain evoked response audiometry revealed mild-to-moderate bilateral hearing loss.

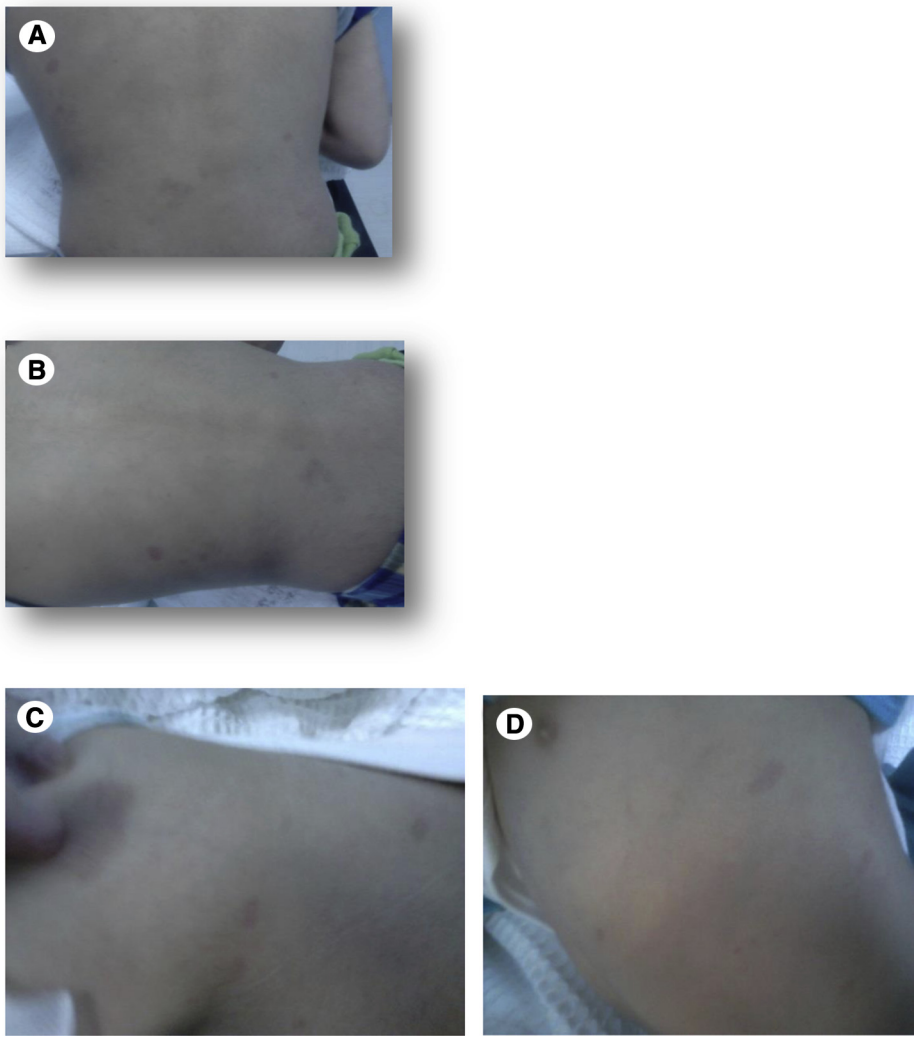

FIGURE 1.
Photographs of cutaneous capillary changes on the back of the Patient 1 (A, B) and torso of the Patient 2 (C, D). These changes became hyperpigmented by age. (The color version of this figure is available in the online edition.)