■ Case vignette

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Epileptic Disorders

STAMBP gene mutation causing microcephaly-capillary malformation syndrome: a recognizable developmental and epileptic encephalopathy

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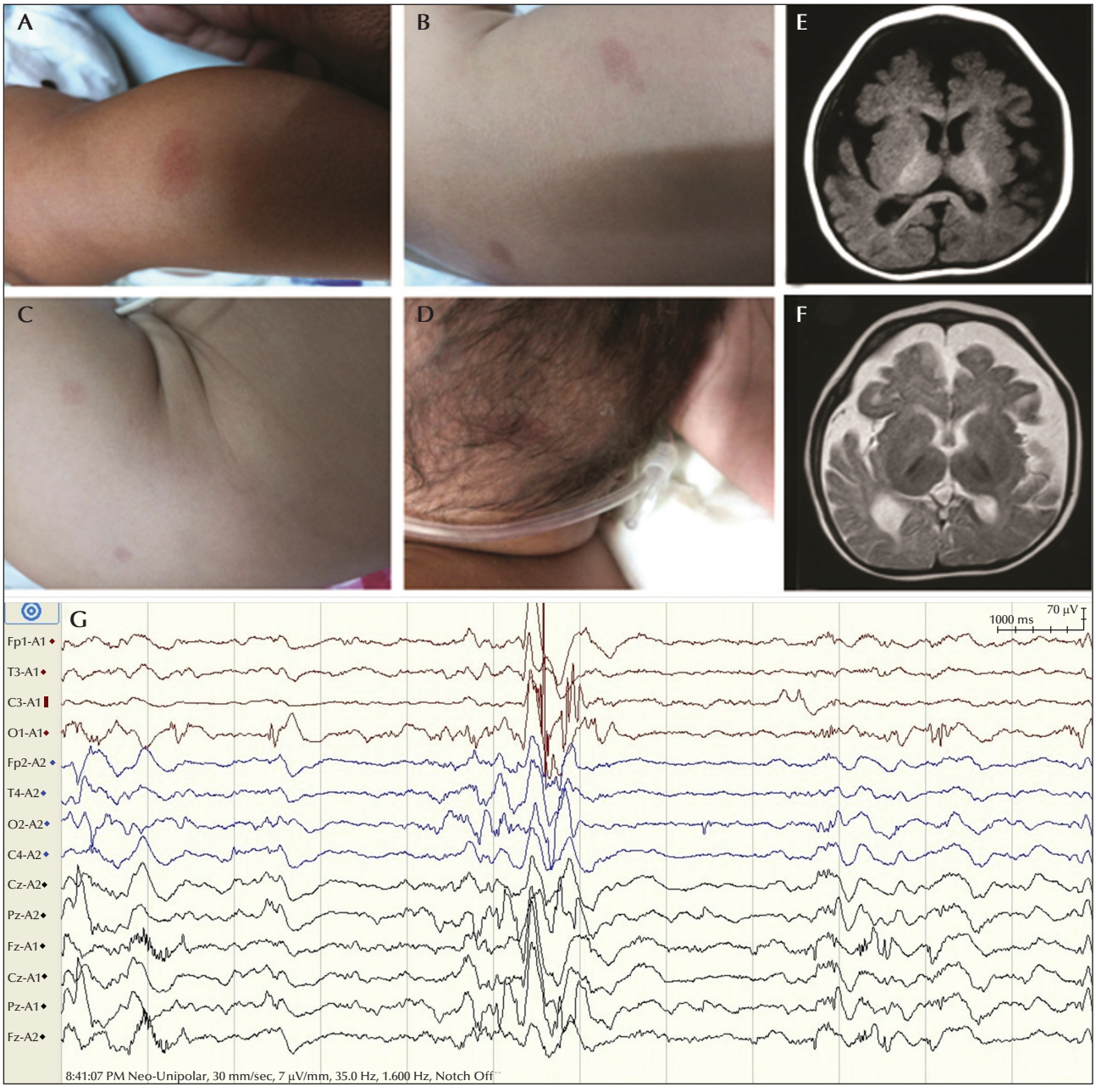
Developmental and epileptic encephalopathy (DEE) represents conditions in which both the underlying genetic aetiology and the ongoing epileptic activity are responsible for developmental delay or regression [1]. Many of these disorders present with seizure onset before three months of age and are known as early-onset DEE. Microcephaly-capillary malformation syndrome (MIC-CAP syndrome; OMIM: 614261) is a recently recognized early-onset DEE for which the characteristic physical findings can clinch the diagnosis [2]. We report a patient with MIC-CAP syndrome with previously unreported mutation and new phenotypic features. This condition can help in understanding the role of the impaired ubiquitin-proteosome pathway (UPP) in epileptogenesis and neurodegeneration.

The patient was a six-month-old male, firstborn to a non-consanguineously married couple with North Indian ancestry, with a normal perinatal period. At one month of age, he started having flexor spasms. By three months of age, focal tonic, clonic, myoclonic and sequential seizures started appearing. On presentation, he had respiratory distress and was encephalopathic. His head circumference was 36.5 cm (-5 to -6 SD) and he had multiple 2 to 15-mm non-blanchable macules distributed over the trunk, limbs and scalp (*figure 1A-D*). Dysmorphic facial features such as sloping forehead, widely spaced eyes, short nose with anteverted nares, low-set ears with increased posterior angulation and micrognathia were noted with no distal limb anomalies. Axial hypotonia, appendicular hypertonia, and brisk deep tendon reflexes were present. Brain MRI showed cortical atrophy with a simplified gyral pattern (*figure 1E-F*). EEG during sleep showed burst suppression with inter-burst interval of 3-5 seconds (*figure 1G*). Due to the presence of recurrent pneumonia, bronchoscopy was performed which revealed pan-airway malacia. Echocardiogram, fundus and BERA were normal. The seizures were refractory to consecutive trials of vigabatrin, topiramate, zonisamide and vitamins. He succumbed to his illness at 18 months of age following an increase in seizure frequency and pneumonia. A novel likely pathogenic homozygous missense variation in exon 4 of the STAMBP (STAM-binding protein) gene (p.Ala99Gly) was detected, which encodes for a deubiquitinating isopeptidase. A protein modelling study demonstrated that this substitution leads to decreased affinity for, and adversely impacts binding to CHMP3 (charged multivesicular body



■ **Figure 1.** Capillary malformation distributed over the limbs (A), trunk (B, C) and scalp (D). T1-weighted (E) and T2-weighed (F) MRI of the brain showing diffuse cerebral atrophy with dilatation of the sulcal spaces. (G) Ten-second sleep EEG epoch showing a burst suppression variant associated with modified hypsarrythmia.

protein 3). This interaction is critical for effective sorting and trafficking of ubiquitinated proteins from endosomes to lysosomes [3]. The methodology and results of the protein modelling study are provided as *supplementary material*.

MIC-CAP syndrome is an extremely rare DEE with the presence of capillary malformation in all cases. Akin to the index patient, the majority of published cases had a triad of neurological symptoms, namely extreme microcephaly with head circumference between -3 to -8 SD, early-onset intractable seizures and severe developmental delay [2, 4, 5]. The presence of pan-airway malacia on bronchoscopy in the index patient is a new feature in MIC-CAP syndrome.

MIC-CAP syndrome is probably the first human disorder confirmed to be caused by congenitally

defective deubiquitination [6]. Due to defective endocytosis of activated receptors such as G protein-coupled receptors and tyrosine kinases, downstream pathways such as PI3-AKT-mTOR and RAS-MAPK are activated, as in various neurocutaneous syndromes. Although the cutaneous manifestations may be explained by RAS and mTOR pathway activation, their contribution to epileptogenesis may be minor. This notion is supported by the failure of vigabatrin in the index patient and ketogenic diet in other reports to control seizures, as mTORopathies significantly respond to dietary therapy and vigabatrin. The absence of cortical malformations (except a simplified gyral pattern) in any of the previous reports and the presence of severe and progressive cortical atrophy also reinforce this.

Intracellular deposition of aggregates of the ubiquitin-conjugated proteins due to defective deubiquitination may lead to induction of apoptosis and increased autophagic flux resulting in neuronal death with resultant progressive microcephaly. This was proven by demonstrating neurodegeneration in stambp-/- mice [7]. Impaired glutamate receptor regulation also may have contributed to the development of drug-resistant epilepsy [6]. Therefore, we may infer that the major mechanism of epilepsy in MIC-CAP syndrome is neurodegeneration secondary to impaired deubiquitination rather than activated mTOR or RAS pathways which may represent downstream effects. Owing to the presence of capillary haemangioma and epilepsy, this disorder is considered a neurocutaneous syndrome by many authors. However, due to the stark differences in clinical presentation, course and underlying pathophysiology, we propose to consider this disorder as an early-onset DEE rather than a neurocutaneous syndrome.

MIC-CAP syndrome adds to the genetic heterogeneity of early-onset DEE which previously was dichotomized as Ohtahara syndrome or early myoclonic encephalopathy. This classification is becoming redundant since many patients such as the index patient cannot be classified into either group and adds little to the aetiological workup. Apart from mutations involving ion channels, early-onset DEE may be caused by alterations in synaptic proteins (STXBP1), the regulation of gene expression (CDKL5), protein modification and translation (PIGA), or cell membrane stabilization (SPTAN1) [8]. The index case adds impairment of the UPP as a possible novel underlying mechanism for DEE. Although alteration of the UPP is implicated in many neurodegenerative diseases such as Alzheimer disease, an early-onset DEE phenotype has never been described. This mechanism may therefore serve as the missing link between epileptogenesis, autism and neurodegeneration. The successful use of the JAK inhibitor, ruxolitinib, in a neonate with deficiency of USP18, a deubiquitinating protease, is an example of the application of precision medicine in congenitally altered UPP [9]. This index case highlights the evolving clinical spectrum associated with STAMBP gene variants as well as STAMBP gene variation in pan-ethnic populations. It also sheds light on the complex interactions of cellular pathways involved in neurodegeneration and epilepsy. ■

Supplementary material.
Summary slides and supplementary material accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
None of the authors have any conflicts of interest to declare

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TEST YOURSELF

(1) What is the diagnostic triad associated with *STAMBP* mutation?

(2) What was the first human disorder reported to be caused by congenitally defective deubiquitinisation?

(3) What is the mechanism of action of ruxolitinib?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.