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Publication Date

2018-07-01

DOI

10.1136/bcr-2018-226246

Peer reviewed

Novel KRIT1/CCM1 heterozygous nonsense mutation (c.715 C>T) associated with cerebral and cerebellar cavernous malformations in a paediatric patient

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Accepted 10 July 2018

To cite: Chen DY, Crawford JR. *BMJ Case Rep* Published Online First: [*please include* Day Month Year]. doi:10.1136/bcr-2018-226246

DESCRIPTION

A 4-year-old Hispanic boy with no significant history presented to the emergency room with 4 days of headache, nausea, vomiting and gait abnormality. Physical exam was significant for cerebellar symptoms. MRI of the brain showed multiple foci of susceptibility, which are suggestive of cavernous malformations with evidence of recent haemorrhagic in the largest cerebellar lesion (figure 1). Magnetic resonance angiogram and MRI of the spine did not show additional lesions. Genetic sequencing revealed a novel heterozygous nonsense nucleotide transition (c.715C>T;pQ239X) of the *CCM1/KRIT1* gene. This mutation predicted a premature stop codon and is expected to be pathogenic. No family history of cavernous malformation was reported for this patient.

Cerebral cavernous malformations (CCMs) are vascular lesions that affect 0.5% of the population. Three genetic loci—CCM1, CCM2 and CCM3—are responsible for nearly 90% of all familiar cavernous malformations.[1] Mutations in the CCM genes are hypothesised to lead to compromised endothelium integrity and abnormal angiogenesis, resulting in vascular malformation.[2] Hispanic Americans, like our patient, have a 20-fold to 100-fold increase in risk compared with the general population, and a well-documented founder mutation (c.1363C>T;pQ455X) has been reported.[3] Only 20%–30% of patients with CCM are symptomatic.[1] While CCM has been well described in adults, the natural history of CCM progression in the paediatric population is not well known; the mean age of clinical onset is 29.7 years.[2] This *CCM1/KRIT1* mutation, identified in our patient, has never been reported. Thus, although less prevalent, in a paediatric patient with characteristic neuroimaging findings of CCM, genetic testing should be considered.

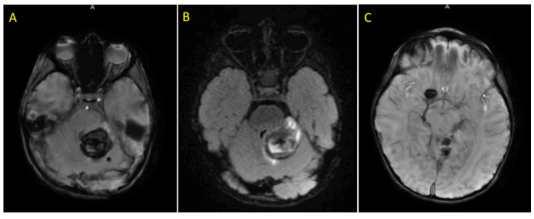

Figure 1 MRI of the brain demonstrates a large heterogeneous lesion in the left cerebellar hemisphere with associated oedema (A: Swan sequence; B: T2 fluid attenuation inversion recovery sequence), and additional lesions, including in the right posterior inferior frontal lobe (C: Swan sequence).

Learning points

- Patients with cerebral cavernous malformations can present with seizures, stroke, headaches or haemorrhage.
- Genetic testing should be considered if the neuroimaging demonstrates lesions suggestive of cerebral cavernous malformations.

Contributors JRC and DYC were responsible for the design, acquisition and interpretation of the data, and writing of the case report. Both authors have reviewed and approved this submission.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Parental/guardian consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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