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Title

Constitutional mismatch repair deficiency (CMMRD) presenting with high-grade glioma, multiple developmental venous anomalies and malformations of cortical development – a multidisciplinary/multicentre approach and neuroimaging clues to clinching the diagnosis.

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Abstract:

Constitutional mismatch repair deficiency syndrome (CMMRD) is a rare cancer-predisposition syndrome associated with a high risk of developing a spectrum of malignancies in childhood and adolescence, including brain tumours.

In this report we present the case of an 8 year old boy with acute headache, vomiting and an episode of unconsciousness in whom brain imaging revealed a high-grade glioma (HGG). The possibility of an underlying diagnosis of CMMRD was suspected radiologically on the basis of additional neuroimaging findings, specifically the presence of multiple supratentorial and infratentorial developmental venous anomalies (DVAs) and malformations of cortical development (MCD), namely heterotopic grey matter.

The tumour was debulked and confirmed to be a HGG on histopathology. The suspected diagnosis of CMMRD was confirmed on immunohistochemistry and genetic testing which revealed mutations in *PMS2* and *MSH6.*

The combination of a HGG, multiple DVAs and MCD in a paediatric or young adult patient should prompt the neuroradiologist to suggest an underlying diagnosis of CMMRD. A diagnosis of CMMRD has important treatment and surveillance implications not only for the child, but also the family in terms of genetic counselling.

Keywords:

Constitutional mismatch repair deficiency syndrome, CMMRD, high-grade glioma, developmental venous anomaly, grey matter heterotopia, malformation of cortical development

Abbreviations:

ACC = Agenesis of the corpus callosum; CM = Cavernous malformation; CMMRD = Constitutional mismatch repair deficiency syndrome; CNS = Central nervous system; DVA = Developmental venous anomaly; EEG = electroencephalography; HGG = High-grade glioma; IDH1 = Isocitrate dehydrogenase 1; MCD = malformation of cortical development

Introduction

Constitutional mismatch repair deficiency syndrome (CMMRD, OMIM: 276300 and ORPHA: 252202) is a rare cancer-predisposition syndrome which occurs as a result of biallelic germline mutations in the *MLH1, PMS2, MSH2 or MSH6* mismatch repair genes. Other names for this entity are brain tumour predisposition syndrome type 1 (BTPS1), mismatch repair cancer syndrome (MMRCS) or biallelic mismatch repair deficiency (BMMRD) (Kim et al. 2020; Abedalthagafi 2018)

It is associated with malignant central nervous system (CNS) tumours in childhood and adolescence. (Kim et al. 2020) Other malignancies associated with CMMRD include haematological malignancies, carcinomas of the gastrointestinal tract and genitourinary system and other malignant tumours such as neuroblastoma and rhabomyosarcoma. A number of non-neoplastic features have also been described in association with CMMRD, some of which are cutaneous and may be apparent on clinical examination such as café au lait spots, areas of skin hypopigmentation, capillary haemangiomas and lupus erythematosus in descending order of frequency. (Wimmer et al. 2014)

We present the case of an 8-year-old boy who presented to his local hospital with acute neurological signs and symptoms in whom MRI of the brain showed a supratentorial high-grade glioma (HGG) and other structural abnormalities, namely MCD and DVAs. The possibility of an underlying diagnosis of CMMRD was raised due to the neuroimaging features and cutaneous findings of café au lait spots. The diagnosis was confirmed on genetic testing.

We briefly discuss the clinico-radiological-pathological characteristics of this syndrome, focusing on the key imaging features.

Case Report:

A previously fit and well 8 year old boy with an unremarkable birth history and normal developmental milestones presented to his local hospital with headache and vomiting. He had been diagnosed with dyslexia and had some difficulties at school. Prior to the onset of these symptoms he was noted to have an altered level of consciousness, thought to be attributable to a partial seizure although this was not recorded on video and he did not undergo electroencephalography (EEG) at the time of presentation. No constitutional or visual symptoms were noted. His sister had a diagnosis of scleroderma.

He underwent a contrast enhanced MRI scan of the brain which revealed a solid intra-axial mass within the left occipital lobe with strong enhancement and restricted diffusion of the solid components and internal necrotic areas. There was surrounding vasogenic peri-tumoral oedema and associated mass effect on the left lateral ventricle (Image 1). In addition, there was sub-ependymal heterotopic grey matter and dysplastic grey matter extending from the right frontal horn to the overlying cortex. Susceptibility weighted sequences demonstrated numerous supratentorial and a large infratentorial developmental venous anomaly with a typical 'Medusa head' appearance (Image 2).

Image 1 and legend (please see end of article)

Image 2 and legend (please see end of article)

He was transferred to our institution for further management. On further clinical examination he was noted to have two café au lait spots on his arm. Maximal safe surgical debulking of the lesion was subsequently performed through a left occipital craniotomy with no complications.

The histopathological features of the tumour were those of a HGG, in keeping with glioblastoma, WHO grade IV. *IDH1* mutation was negative. The Ki67 proliferation index was very high. Methylation profiling of the tumour failed. There was immunohistochemical loss of expression of *PMS2* with focal loss of *MSH6* and *MSH2* and relative preservation of *MLH1* expression.

The immunohistochemistry findings, in combination with the clinical and radiological findings were highly suggestive of a diagnosis of CMMRD.

The diagnosis was confirmed on genetic testing which revealed abnormalities in *PMS2* variant coding 73C>T and variant protein p.(Gln25*) and *MSH6* (NM_000179.2) c.718C>T p.(Arg240*) 43% pathogenic chromatin remodelling/DNA methylation. The family elected not to undergo further genetic testing.

Discussion:

CMMRD is rare, with approximately 200 reported cases in the literature. The most common malignancies associated with CMMRD are haematological malignancies, brain tumours and carcinomas of the gastrointestinal and genitourinary systems. Pre-malignant and non-malignant manifestations are also described and are a part of the diagnostic criteria compiled by the European Consortium 'care for CMMRD' (C4CMMRD). (Wimmer et al. 2014) Phenotypically, the features of CMMRD can overlap with neurofibromatosis type 1, and more recently an overlap with tuberous sclerosis complex has been described. (Shapira Rootman et al. 2020)

HGGs account for 26% of all malignancies in patients with CMMRD, usually occurring in the first two decades of life. (Vasen et al. 2014) (Wimmer et al. 2014) In addition to HGGs, low-grade gliomas, medulloblastomas and other embryonal tumours have also been described in association with CMMRD. (Amayiri et al. 2016) (Bakry et al. 2014) (Therkildsen et al. 2015)

The presence of a HGG at the age of less than 25 years, and the presence of >=2 hyperpigmented skin alterations over 1cm score two points each on the diagnostic criteria developed by the C4CMMRD consortium. The total score was therefore four in this case. A total score of 3 or more indicates that testing for CMMRD should be undertaken.

There have been case series describing neuroimaging abnormalities in CMMRD in addition to HGG. These include DVAs, grey matter heterotopia and structural abnormalities such as agenesis of the corpus callosum (ACC).

DVA is the most common brain vascular malformation in the general population with an incidence of up to 2.6% in autopsy series and 6.4% in imaging series. (Sarwar and McCormick 1978) (Gökçe et al. 2014) DVAs in the brain are usually incidental neuroradiological findings, but may present with symptomatic thrombosis, intracranial

haemorrhage and seizures. DVAs have been described in association with other vascular malformations, particularly cavernous malformations (CM). (Ruíz et al. 2009)

DVAs have also been described in association with CMMRD. (Shiran et al. 2018) In a recent case series of 10 paediatric patients (age range 1-12 years, mean age 6.5 years) from 3 families with confirmed CMMRD undergoing neuroradiological surveillance, multiple DVAs (range 2-7 per patient) were observed in all 10 patients. Three of these patients did not have a CNS tumour, whilst the remainder had either glial tumours (four HGG, one gliomatosis pattern diffuse glioma), medulloblastoma (one patient) and embryonal tumour not otherwise specified (one patient). Non-treatment related CM were also present in two of these patients, one of which was not associated with the DVA. There was no correlation between the location of the tumour and the DVA. (Shiran et al. 2018)

Subependymal or periventricular nodular grey matter heterotopia is a MCD which occurs due to abnormal neuronal migration. It is the most common type of heterotopia. (Barkovich and Kuzniecky 2000) It may be an isolated abnormality, or occur in association with other structural brain abnormalities. (Abdel Razek et al. 2009) In a case series of three paediatric patients with a genetic diagnosis of CMMRD, two were noted to have subependymal grey matter heterotopia. Further structural brain abnormalities were also present in these patients including interhemispheric cysts in both patients and ACC in one patient, who subsequently developed a glioblastoma. (Baas et al. 2013)

ACC has also been described in association with *PMS2* mutation in two other case reports, one of which also had a concurrent mutation in the DICER1 gene. (Cheyuo et al. 2017)(Gururangan et al. 2008)

No further structural brain abnormalities were present in this case. To our knowledge, there are no further published case series or reports describing an association between grey matter heterotopia and CMMRD

Whilst the outcomes in CMMRD are poor, there are studies examining the potential for novel treatments such as immune checkpoint inhibition which may have implications for glioblastoma and other hypermutant cancers occurring as a result of CMMRD. (Bouffet et al. 2016)

Conclusion:

This case adds to the existing literature by demonstrating an association between HGG, multiple DVAs and MCD in a case of genetically confirmed CMMRD in a paediatric patient. To our knowledge, only two cases of CMMRD associated with grey matter heterotopia have been previously described.

This constellation of imaging findings in a child, adolescent or young adult, in the appropriate clinical context should prompt the neuroradiologist to raise the possibility of the diagnosis of CMMRD, which can guide further work-up. A correct and timely diagnosis of CMMRD can have implications for treatment, ensuring that the patient is kept under surveillance as per C4CMMRD guidance and also in terms of genetic counselling for the family.

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Images and legends:

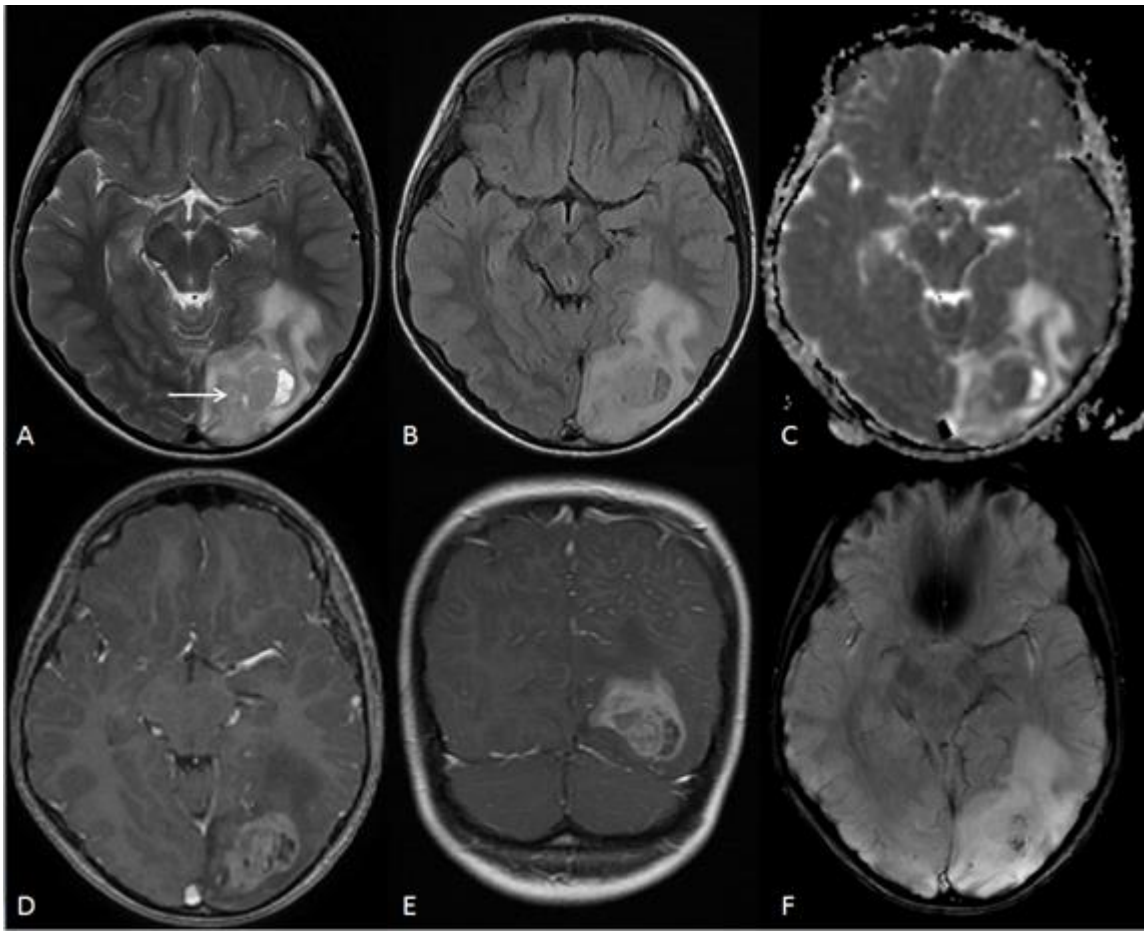

Image 1: Pre-operative MRI. Top row (A) axial T2-weighted (B) axial T2 FLAIR-weighted and (C) axial apparent diffusion coefficient. Bottom row (D) axial T1-weighted post-contrast (E) coronal T1-weighted post-contrast and (F) axial susceptibility weighted sequences.

There is a solid intra-axial mass within the left occipital lobe with strong enhancement of the solid components and internal necrotic areas. The enhancing component of the lesion shows diffusion restriction. There is surrounding vasogenic peri-tumoral oedema and associated mass effect on the left lateral ventricle. The imaging findings are most in keeping with a high-grade glioma.

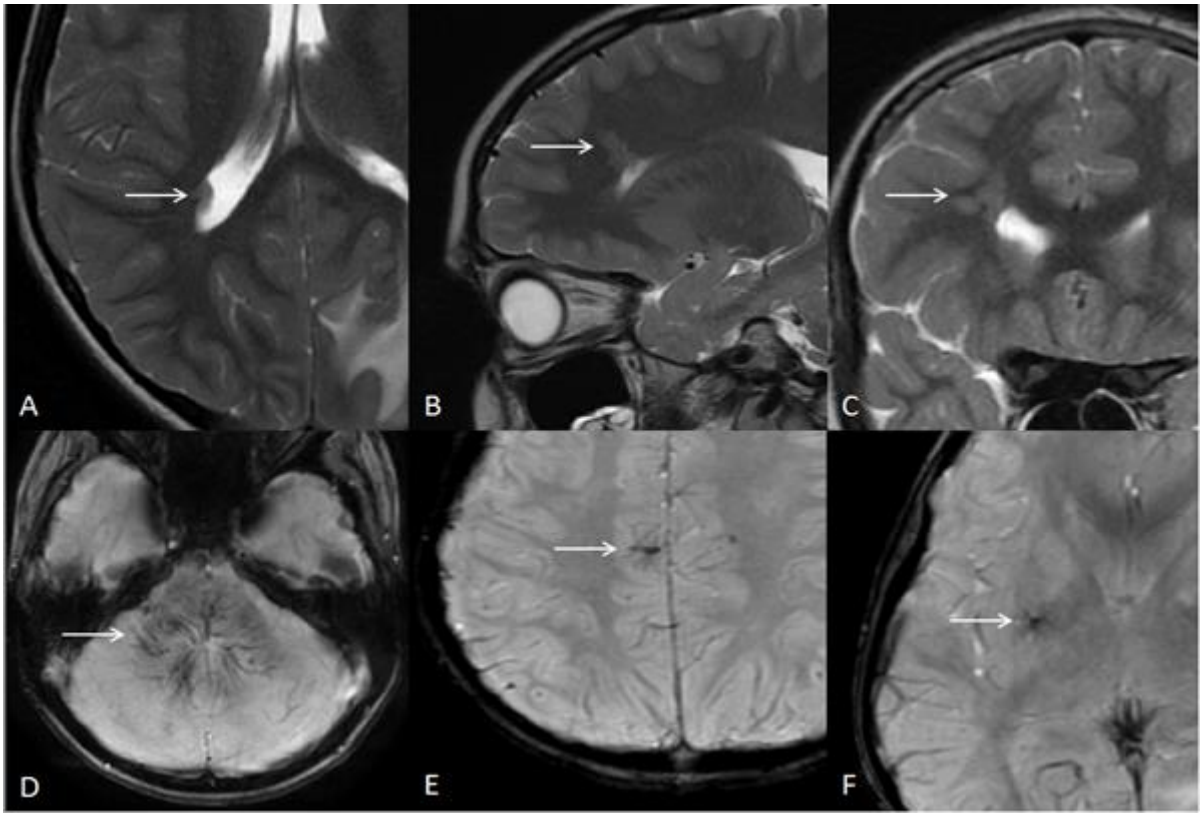

Image 2: Additional imaging clues. Top row (A) axial T2-weighted imaging demonstrating sub-ependymal heterotopic grey matter (B) sagittal T2-weighted and (C) coronal T2-weighted imaging demonstrating dysplastic grey matter extending from the frontal horn to the overlying cortex. Bottom row (D, E and F) axial susceptibility weighted sequences demonstrate numerous supratentorial and a large infratentorial developmental venous anomaly (DVA). The infratentorial DVA has a typical 'Medusa head' appearance. The combination of findings is suggestive of CMMRD.