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Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations – a rare but important differential diagnosis of cerebral vasculitis and demyelination

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ABSTRACT

Background: Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S) is a rare hereditary vasculopathy with an autosomal dominant inheritance pattern. RVCL-S may pose diagnostic challenges due to findings overlapping with vasculitis and demyelinating disorders.

Case presentation: We present the case of a 41-year-old woman with progressive neurological symptoms and no systemic manifestations. Following initial suspicion of demyelination the presence of calcifications and confluent white matter lesions prompted further investigation including genetic testing which revealed a TREX1 mutation on chromosome 3, confirming RVCL-S.

Conclusions: This case underpins the significance to consider RVCL-S in patients with syndromes suggestive of atypical demyelination or cerebral vasculopathy.

Introduction

RVCL-S can mimic brain tumors, central nervous system (CNS) vasculitis, and tumefactive demyelinating diseases. (Richards et al., 2007) The radiological appearance can range from non-specific periventricular and subcortical punctate hyper-intense lesions on T_2 weighted magnetic resonance imaging (MRI) with or without associated enhancement on T_1 weighted scans following Gadolinium-DTPA injection. Additionally, imaging may demonstrate rim-enhancing mass-like lesions, often with intra-lesional calcifications. Diffusion-weighted MRI typically shows restriction of water movement. (Hoogeveen et al., 2021) Early recognition of RVCL-S enables genetic counselling of family members and avoids inadequate treatments, such as immunotherapies.

Here, we report a case where the diagnostic dilemma was ultimately solved after the patient was enroled in the UK 100 Genome Project, which revealed a novel three prime repair exonuclease 1 gene (TREX1) mutation. None of the patient's first-degree relatives, who are all asymptomatic, have been tested for the mutation so far.

Case presentation

A 41-year-old woman was first seen in our hospital's neuroinflammatory clinic in 2012 following referral by a general neurologist. She presented with motor and sensory symptoms affecting her left-sided limbs, leading to difficulties walking. She denied any visual symptoms. Upon exploration of the patient's clinical history, it became apparent that her difficulties walking started about seven years earlier. One year prior to referral, she had started using a cane. In addition, she reported an 18-month history of urinary hesitancy and constipation requiring laxatives. Her only other past medical history was asthma. Family history revealed that her maternal grandmother died prematurely, of unknown cause. Additionally, her mother died aged 39 following multiple cerebral infarcts. She had two affected aunts; one with a suspected diagnosis of multiple sclerosis and the second with a brain tumour. Neither of these diagnoses were confirmed. She has a son who is currently having regular clinical follow-up, however, so far has declined the offer of genetic testing (Fig. 1).

On examination, she had a tri-paretic syndrome affecting her left upper and lower limbs. MRC power grades were 3–4/5 in the affected limbs. Reflexes were brisk in line with an upper motor neuron syndrome. Plantar responses were bilaterally extensor. There was no sensory impairment, and cranial nerve function was normal.

The impression was that this was a chronic progressive CNS disorder with no relapsing features. Initially, the syndrome was thought to represent primary progressive multiple sclerosis (MS).

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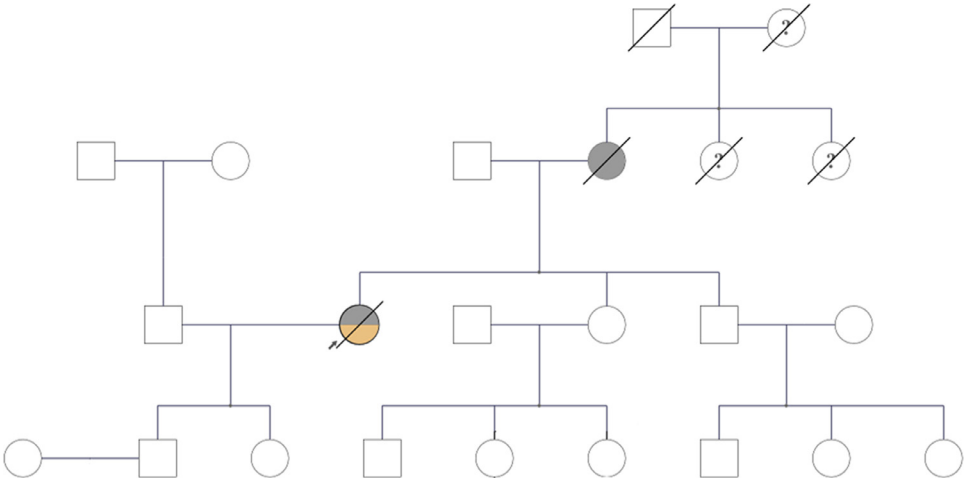

Fig. 1. The pedigree structure of a TREX1 family; The affected patient is represented as an orange and grey circle. Deceased patients with neurological presentation and no confirmed diagnosis are annotated. The arrow points to the patient described in this report.

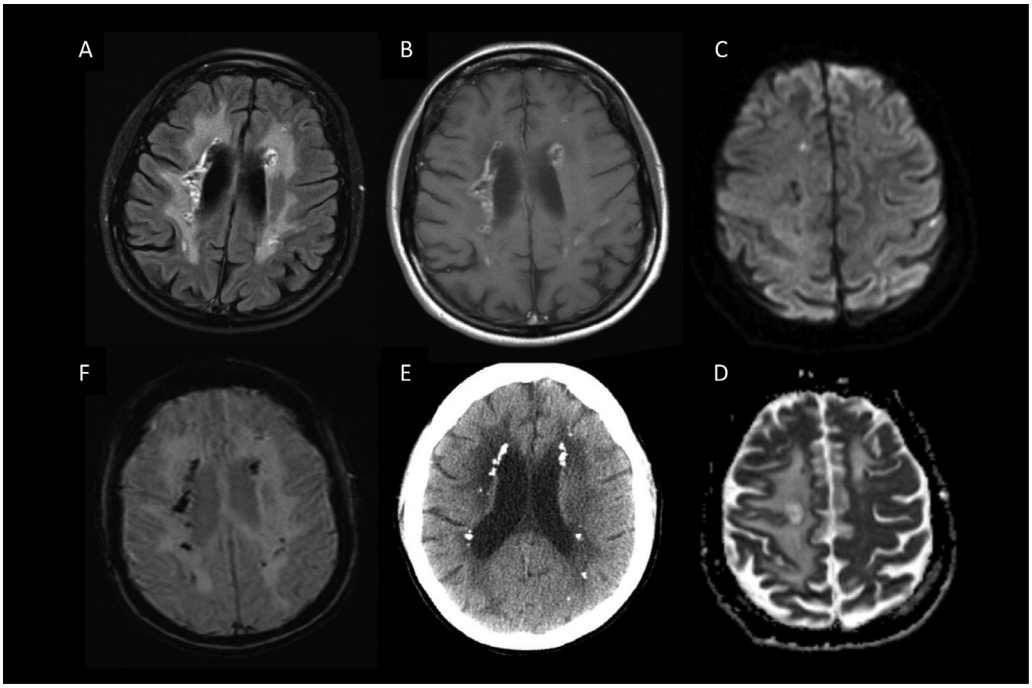

Fig. 2. Selected axial computer tomography (CT) and magnetic resonance (MR) images demonstrate confluent bilateral subcortical and deep white matter signal abnormality. Fluid-attenuated inversion recovery (FLAIR, A) with multiple focal areas of contrast enhancement (post-contrast T_1, B); punctate foci of diffusion restriction on diffusion weighted imaging (DWI, C and apparent diffusion coefficient, D); multiple calcifications on CT (E) and susceptibility weighted MR imaging (SWI, F).

Investigations were normal for haematology, liver and renal function, electrolytes, c-reactive protein and thrombophilia screen, and autoimmune serology. Cerebrospinal fluid analysis showed two lymphocytes/μL, normal protein, glucose ratio, and IgG index. She had normal visual evoked potentials .

Her initial MRI in 2011 demonstrated confluent diffuse white matter lesions. In the opinion of the consultant radiologist involved at the time, the imaging appearances were most in keeping with acute disseminating encephalomyelitis (ADEM). However, the clinical presentation with chronic deterioration, and no recovery, were not in line with this condition.

The patient then presented again with acute worsening of her left arm and leg power. Her presentation at the time led to the consideration of a stroke. A subsequent CT head demonstrated what appeared to be calcification within the white matter lesions previously detected on the MRI brain. Follow-up MRI showed expansion of bilateral white matter lesions affecting both hemispheres and conspicuous involvement of the posterior fossa (Fig. 2). These imaging appearances raised the possibility of leukodystrophy, and the patient went on to have genetic testing as a part of the 100,000 Genome Project. Testing demonstrated that she was heterozygous for TREX1 C.868dup, which confirmed the diagnosis of TREX1 related disorder. The patient passed away in 2014. The next of kin declined an autopsy.

Discussion

RVCL-S is a rare inherited disease. It develops due to a frameshift mutation in TREX1 at the C-terminus, which interferes with the localization of the TREX1 protein. (Hasan et al., 2015; Richards et al., 2007) TREX1 encodes for the DNAse III enzyme, which is thought to play a role in innate immunity. (Hasan et al., 2015; Richards et al., 2007) Our patient had the TREX1 mutation c868dup, which is associated with patho-

logical loss of function of TREX1. The most common presenting features of RVCL are vasculopathy of medium and small vessels, although with sparing of the leptomeningeal and extraparenchymal arteries. In addition, there are ischaemic and fibrinoid necrosis of the white matter. (Raynowska et al., 2018; Hasan et al., 2015; Stam et al., 2016)

RVCL can present with various neurological symptoms including seizures, cognitive impairment, and focal neurology. Interestingly the vasculopathy may present initially in the retina, but without firm neurological symptoms may be diagnosed as hypertensive or diabetic retinopathy. (Raynowska et al., 2018; Stam et al., 2016) This may also pose a route to early diagnosis, although suspicion from the family history would likely need to be made available given the prevalence of hypertensive and diabetic complications. (Raynowska et al., 2018)

Based on the presenting symptoms and some of the imaging appearances, RVCL-S may be misdiagnosed as tumefactive MS, vasculitis, or malignancy, and as such, patients may undergo brain biopsy. (Raynowska et al., 2018), (Macaron et al., 2021) Given the rarity of the diagnosis, some resemblance with features of cerebral vasculitis and MS may lead to misdiagnosis and, thus, inadequate treatment. In the two cases of TREX1 described by Raynowska et al. (2018), the patients underwent a brain biopsy with inconclusive results. They received methylprednisolone for presumptive diagnoses of tumefactive inflammatory brain lesions. Ultimately, genetic testing confirmed the diagnosis of RVCL-S due to a TREX1 gene mutation (c.703dupG[V235G*fs*]). In comparison, our patient did not exhibit any systemic features of RVCL-S and had a mutation at a different nucleotide region than previously reported (C.868dup).

Indeed, in our patient, the initial impression resembled primary progressive MS. Only the attendance for stroke-like symptoms prompted a CT head scan that showed widespread calcifications, a feature also observed by Macaron et al. (Macaron et al., 2021) Calcification is not a feature of MS, and this should lead to review in patients with a syndrome suggestive of demyelination. Early recognition of TREX1 not only alleviates uncertainty for the patient. It also avoids unnecessary, often invasive, investigations and treatment. For example, although not a feature of this case, a presumed diagnosis of tumefactive MS may lead to immunotherapy, exposing the patient to risks of infections and other treatment-associated adverse events. Early diagnosis enables appropriate counselling and genetic testing of family members. Importantly, although no specific treatments are available yet, a phase 2 trial is currently underway to test whether Crizanlizumab, a humanised monoclonal anti p selectin antibody, that can prevent leucocyte adhesion to the vascular endothelium, thereby reducing microvascular occlusion with the endpoint changing in fluid-attenuated inversion recovery (FLAIR) MRI in patients with RVCL (NCT04611880). (Crizanlizumab for treatment of Retinal vasculopathy with cerebral leukoencephalopathy, 2021)

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Declaration Competing of Interest

The authors declare no conflict of interest. The authors have nothing to disclose.

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