Leukoencephalopathy caused by a 17p13.3 microdeletion

INTRODUCTION

Inherited white matter disorders (IWMDs) comprise a group of genetic disorders with onset from childhood to late adulthood in which there is degeneration of central nervous system white matter tracts. They are clinically and genetically heterogeneous. In adults, there may be a wide variety of clinical manifestations including cognitive decline, spasticity and ataxia, and the general course is progressive. Despite advances in imaging, phenotyping and genetic analysis, at least one-third of patient with suspected adult-onset IWMDs are refractory to diagnosis—hindering prognostication, reproductive decision making and the identification of disease-modifying treatments.[1]

In this report, we describe a novel phenotype of extensive, confluent, paucisymptomatic adult-onset leukoencephalopathy in adults caused by a 248 kb microdeletion of 17p13.3, which unlike other similar microdeletion syndromes has no impact on psychomotor development and has not been associated with any syndromic or extraneurological features so far.

Case descriptions

The proband (patient 1) is a woman in her 30s referred with a history of headache. She had no other medical history. Her perinatal and early childhood history was unremarkable, and she met all psychomotor milestones, attended university and excelled at sport. Her neurological examination (including funduscopy) was normal aside from mild essential tremor, and her general examination revealed only mild hypermobility. A brain MRI revealed confluent white matter changes. Routine blood and cerebrospinal fluid white matter investigations[2] were negative, with no evidence of systemic organ

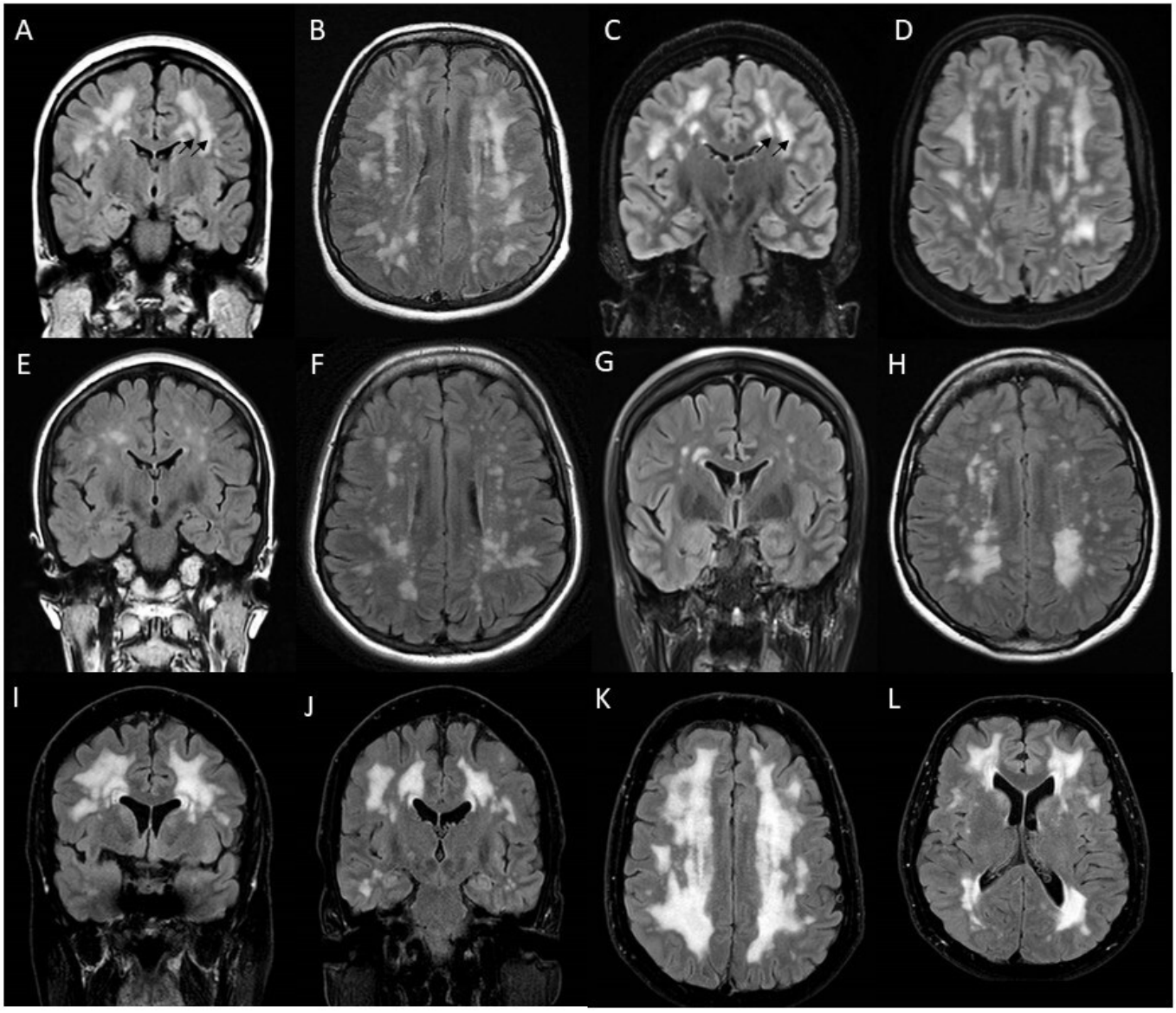

Figure 1 Coronal and axial fluid attenuated inversion recovery (FLAIR) imaging for patient 1 at first presentation (A, B) and after a 5-year interval (C, D) demonstrating extensive deep white matter hyperintensity arranged in concentric band-like distributions (best seen on the coronal plane). Further coronal and axial FLAIR images for the patient 2 (E, F) and patient 3 (G, H) show a similar distribution of white matter changes. More extensive, confluent FLAIR hyperintensity is seen in patient 4 (I, J, K, L), the non-symptomatic father again with sparing of the U-fibres, corpus callosum, external capsule, anterior temporal lobe and infratentorial compartment.

involvement. Renal function was normal.[2] The proband's younger sister (patient 2) was already known to have similar white matter changes (having had an MRI for head injury), and also suffered from migraine. As a result, a genetic cause was suspected, and the remainder of the family were screened.

The proband's older sister and father (patients 3 and 4)—neither of whom experienced migraine or other neurological symptoms—were found to also exhibit confluent white matter changes (figure 1). The rest of the family was unaffected clinically and radiologically.

All affected family members completed higher education and held high functioning jobs. There is no history of prenatal or postnatal abnormality, psychomotor disturbance, seizure or facial dysmorphism. Common to all affected individuals was hypermobility, with no other neurological or extraneurological features on examination.

In his mid-60s, patient 4 developed subacute gait problems culminating in repeat imaging that revealed multifocal high-grade glioma. He passed away soon after diagnosis.

Imaging abnormalities

All patients exhibited extensive, confluent, supratentorial deep white matter FLAIR hyperintensities arranged in apparent concentric bands with sparing of the U-fibres, corpus callosum, external capsule and infratentorial region (figure 1). In patients 2 and 4 there was mild posterior-temporal lobe involvement but in patients 1 and 3 the temporal lobe was spared. The changes were static over longitudinal imaging. There was no evidence of atrophy and the cortex was spared. None of the patients exhibited lacunes or diffusion abnormalities and there were no microbleeds on susceptibility weighted imaging. Spinal cord imaging, where available was normal. Magnetic resonance spectroscopy was not performed.

Genetic testing

We initially tested the proband with a targeted 75-gene panel for genetic variants associated with adult-onset white matter disorders, which was negative. All family members then underwent whole exome sequencing which did not identify any segregating likely pathogenic variants. The proband and her parents then underwent trio whole genome sequencing. This revealed heterozygosity for a 248 kb microdeletion on the short arm of chromosome 17 between position 1 829 683 and 2 078 186 (online supplemental figure 1). The proband's siblings underwent targeted chromosomal microarray analysis which confirmed segregation. This deletion has not been found in controls.

DISCUSSION

We describe a novel syndrome of minimally symptomatic adults with florid, static leukoencephalopathy secondary to a 17p13.3 microdeletion. Microdeletion syndromes are not commonly associated with adult-onset IWMDs, and microarray analysis is not routinely performed. Typically, microdeletions that cause white matter abnormalities (1p36, 2q23.1, 6p25, 18q23 and 22q11.2) are detected in childhood and are associated with significant developmental abnormalities.[3] Larger deletions in the 17p13.3 genomic region also cause white matter changes in children. Well-characterised phenotypes associated with these deletions, such as Miller-Dieker syndrome (caused by deletions that include genes *YWHAE* and *PAFAH1B1*) and isolated lissencephaly sequence (caused by deletions involving only *PAFAH1B1* but not *YWHAE*) are also typically associated with significant symptoms including dysmorphic features, developmental delay and premature life expectancy.[4]

Emrick *et al* recently described six patients with 17p13.3 microdeletions between the *YWHAE* and *PAFAH1B1* loci (online supplemental figure 1).[5] These patients also presented with white matter abnormalities without significant associated intellectual disability. However, the patients described by Emrick *et al* are children who presented with dysmorphic facies, behavioural changes or extraneurological features, unlike the adults described here.

Notably, all deletions in the Emrick *et al* cohort were larger than the deletion we report, explaining the dysmorphism and other syndromic features in their patients (online supplemental figure 1). Interestingly, the smallest region of overlap between the Emrick *et al* deletions (Chr17:1770860-2099130) is very similar in size and location to the deletion described here, indicating that this region is responsible for causing a unique static leukoencephalopathy.[5]

There are 10 RefSeq genes within the deletion we report (online supplemental figure 1). *RTN4RL1* and *SMG6* are the only genes with specific expression in the brain, with the others expressed at low levels. *RTN4RL1* regulates axonal and dendritic growth and contributes to normal axon migration, which is of interest given the appearance of concentric hyperintensities in our patients. *RTN4RL1* has a high pHaplo score (0.99), indicating a high likelihood of haploinsufficiency. Deletions of its paralog *RTN4R* cause white matter abnormalities and have been associated with various neurological and psychiatric disorders.[3] *SMG6* (pHaplo score 0.99) encodes a component of the telomerase ribonucleoprotein complex, which plays a role in the nonsense-mediated messengerRNA decay pathway.

HIC1 (pHaplo score 0.98) is a transcriptional repressor and tumour suppressor gene. It has been implicated in precartilaginous tissue and muscle development, and may play a role in the joint laxity seen in both the patients described here and by Emrick *et al*.[5 6]

CONCLUSION

This report contributes to the literature on the genetic basis of white matter disorders. Although microdeletions are not a frequent cause of adult-onset IWMDs, in cases refractory to genetic diagnosis, consideration should be given to whole genome sequencing, chromosomal microarray or both.

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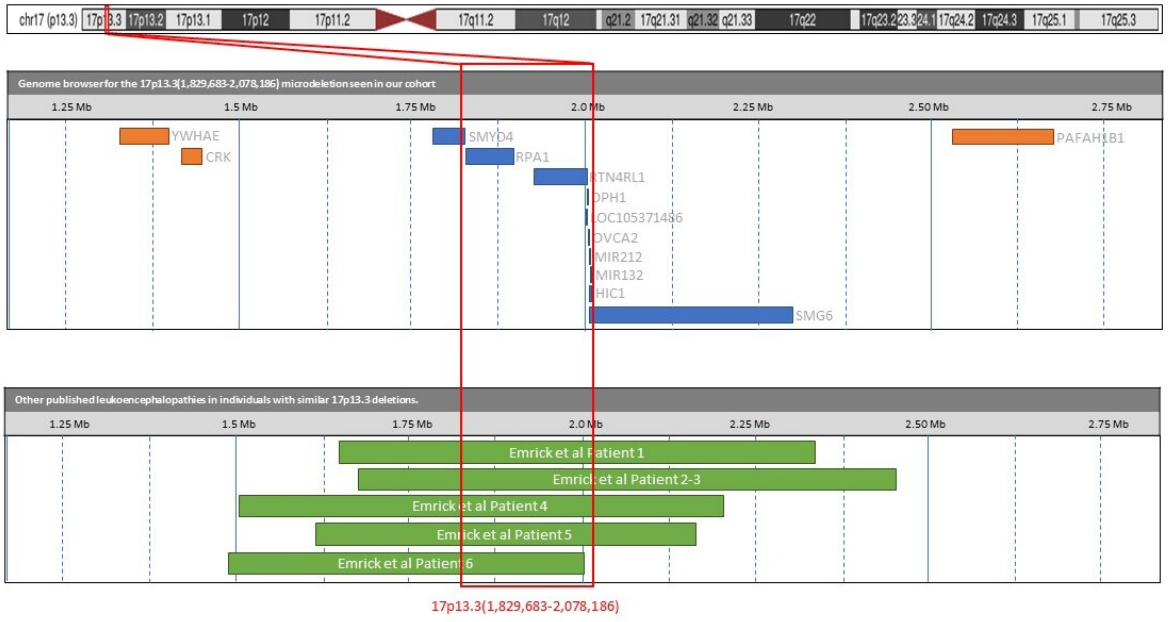
chr17 (p13.3)
17p13.3
17p13.2
17p13.1
17p12
17p11.2
17q11.2
17q12
q21.2
17q21.31
q21.32
q21.33
17q22
17q23.2
23.3
24.1
17q24.2
17q24.3
17q25.1
17q25.3
Genome browser for the 17p13.3(1,829,683-2,078,186) microdeletion seen in our cohort
1.25 Mb
1.5 Mb
1.75 Mb
2.0 Mb
2.25 Mb
2.50 Mb
2.75 Mb
YWHAE
CRK
SMYD4
RPA1
TN4RL1
DPH1
OC105371486
DVCA2
MIR212
MIR132
HIC1
SMG6
PAFAH1B1
Other published leukoencephalopathies in individuals with similar 17p13.3 deletions.
Emrick et al Patient 1
Emrick et al Patient 2-3
Emrick et al Patient 4
Emrick et al Patient 5
Emrick et al Patient 6
17p13.3(1,829,683-2,078,186)