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CADASIL AND BIPOLAR AFFECTIVE DISORDER

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SUMMARY

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is a rare monogenic disorder caused by mutations in the NOTCH3 gene. The clinical features are primarily neurological, which include recurrent transient ischaemic attacks, strokes, and migraines. However, psychiatric manifestations which mainly include mood disturbances have also been reported in CADASIL. Manic symptoms and bipolar disorders are rarely documented in CADASIL and existing reports generally lack detailed descriptions of the psychiatric evaluation.

We discuss a case of Bipolar Affective Disorder (BD) in a British woman with a family history of CADASIL.

This case provides insight into the diagnosis and management of BD as well as the possible underlying aetiologies that should be considered. The similarities between BD and CADASIL in terms of imaging, genetic, and therapeutic aspects raise the possibility of common dysfunctional pathways. BD in CADASIL may warrant greater consideration by both psychiatrists as well as non-psychiatric specialists and further studies are required to understand the pathological significance.

Key words: *CADASIL - Bipolar Affective Disorder - EUPD*

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INTRODUCTION

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is a rare inherited cerebrovascular disease that develops due to mutations in the NOTCH3 gene on chromosome 19p13.1 (Di Donato et al. 2017).

The clinical features, age of onset, and progression of CADASIL are variable. Clinically, it is characterised by mid-adulthood onset, primarily with neurological features including recurrent subcortical ischemic events with white matter hyper-intensities visible on magnetic resonance imaging (MRI) and migraine with aura (Dichgans et al. 1998). This is often accompanied by a varying degree of cognitive decline. Although the clinical features have a neurological preponderance, CADASIL is also characterised by psychiatric manifestations, reported in approximately one third of patients in CADASIL cohorts (Adib-Samii et al. 2010). These mainly include, mood disturbances, anxiety disorders, and personality disorders, with psychotic symptoms also being described (Chabriat & Bousser 2007). Most patients are affected by major depression, with other important psychiatric conditions such as bipolar affective disorder (BD) rarely being described otherwise (Valenti et al. 2008). The reported frequency of BD in CADASIL patients varies widely in the literature from 2% in one meta-analysis (Valenti et al. 2008) to 26% in a retrospective cohort study (Valenti et al. 2011). BD, especially BD type II, is difficult to diagnose correctly and is often underdiagnosed. As many as 40-50% of cases are misdiagnosed as unipolar depression (Benazzi 2007), which may be related to heterogeneity in the disorder. In the CADASIL literature, the diagnostic criteria used for BD are often inconsistent or unreported, which may account for the discrepancies. This highlights a need for clinicians to be aware of the possible psychiatric manifestations of CADASIL, as well as the need for psychiatrists to consider CADASIL as a differential diagnosis.

Despite the significant morbidity of BD in CADASIL, the frequency is likely to be underestimated (Chabriat & Bousser 2007). Although CADASIL is increasingly recognised in the neurological literature, fewer studies go beyond solely reporting on the existence of the associated mood disturbances such as BD among its cardinal symptoms (Valenti et al. 2008). Comparable imaging and genetic findings exist between BD and CADASIL, which raises the possibility that the two disorders share common pathogenic mechanisms. In this report, we discuss a case of BD in a British woman with a family history of CADASIL. Thus, we expand on the clinical approach to BD and the diagnosis of CADASIL.

CASE PRESENTATION

Having obtained full informed consent, we describe a case of a 41 year old British woman, who was admitted to the Acute Day Treatment Unit (ADTU). Prior to her admission to ADTU, there had been an episode of her having taken an overdose. She gave a history of alleged emotional and sexual abuse and described having pervasive features of Emotionally Unstable Personality Disorder (EUPD). Additionally, on careful history taking, it transpired that she had been experiencing a number of episodes of manic and hypomanic symptoms which usually lasted around 4-7 days and were followed

by longer periods of depressive symptoms. Additionally, there were mixtures of manic, hypomanic, and depressive symptoms. Her misuse of alcohol was much more apparent during manic/hypomanic periods. She further stated that she often took to alcohol to 'bring herself down' during her manic/hypomanic periods. She was taking 100 mg of Sertraline daily and 200 mg of Quetiapine daily. Indeed, she had noticed when she was on a higher dose of Sertraline (200 mg daily), she experienced more frequent manic/ hypomanic episodes with rapidity of cycling. She was diagnosed with EUPD and BD (rapid cycling type), with a differential diagnosis of BD type II. She was well aware that her father died of diagnosed CADASIL, having had a major stroke in his 50s. She was also aware that her paternal grandmother also had a stroke at a relatively young age. Furthermore, she knew that CADASIL is an autosomal dominant genetic condition and that she had a 50% chance of inheriting it. This was clearly troubling her and she was keen to have genetic testing to check if she had CADASIL. On her request, and with the assistance of her GP, we arranged for the genetic testing from the regional genetic service who carried out the test after counselling.

Fortunately, she was found not to have inherited the CADASIL gene.

DISCUSSION

CADASIL is a rare monogenic disease caused by mutations in the NOTCH3 gene on chromosome 19p13.1 that can present with a range of symptoms including: stroke, migraine with aura, cognitive impairment, and psychiatric disturbances. The most frequently reported psychiatric disturbances are mood disturbances (9–41%) (Valenti et al. 2008), including BD. BD is a heterogeneous disorder and the continuum/spectrum approach to mood disorders has been introduced to account for this as the research on BD subtypes continues to expand. Our current case of BD was suspected to be a manifestation of CADASIL based on the family history of the condition. However, this significant differential diagnosis was excluded by genetic testing that was initiated following psychiatric evaluation. This case has highlighted the dynamic process involved in the diagnosis of BD as well as issues surrounding the psychiatric manifestations of the suspected underlying organic aetiology of CADASIL.

A small number of case reports have explored the presentation of mood disorders in CADASIL. CADASIL presenting with symptoms of mania have been discussed in case reports by Kumar & Mahr (1997) and Park et al. (2014). Leyhe et al. (2005) and Wang et al. (2017) have elaborated on cases with hypomanic and depressive features. Gamakaranage & Chang (2012) previously described a CADASIL patient with personality changes (including mood swings and aggressive behaviour) but without manic features. In a number of these reports, a detailed description of the psychiatric work-up and treatment was not included (Gamakaranage & Chang 2012, Kumar & Mahr 1997).

Similarities in the genetic findings have been described between BD and CADASIL. While we do not suggest that these illnesses are equivalent, understanding the correlations of BD with CADASIL provides insight into dysfunction within gene networks common to both disorders. BD is reported to have a high degree of heritability but is thought to be a multifactorial disease, stemming from environmental contributions and multiple genes that have not yet been identified (Craddock & Sklar 2013, Muller-Oerlinghausen et al. 2002). Previous genetic linkage analyses investigating NOTCH3 as a candidate gene for BD have yielded negative results (Ahearn et al. 2002). However, more recently, integrative approaches have identified gene-expression associations between the Notch signalling pathway and BD (Pedroso et al. 2012). It may be the case that patients with BD exhibit less distinct downstream dysfunction in the Notch3 signalling pathway in comparison to CADASIL.

The association of BD with CADASIL provides insight into the organic basis and possible therapeutic avenues for psychiatric illnesses once widely considered to be functional disorders lacking an observable disease process. MRI has revealed an increased prevalence of white matter hyper-intensities in patients with BD compared to normal controls (Altshuler et al. 1995), which has been used as an endophenotype in the disorder (Sarıçiçek et al. 2016). The white matter lesions affecting the fronto-limbic and fronto-striatal pathways may contribute to developing BD in later life. Notably, these imaging findings in BD resemble those reported in CADASIL (Di Donato et al. 2017) and the Notch pathways have also been suggested as a causative factor (Mahon et al. 2010). Most of these white matter hyper-intensities are thought to arise from focal cerebral ischemia (Thomas et al. 2002) which suggests that ischaemic episodes may contribute to the pathophysiology of both disorders. However, it must be noted that BD and other mood disorders that may arise in CADASIL could be a consequence of the disabling neurological function reported in many cases.

The arteriopathy of CADASIL is characterised by the progressive degeneration of vascular smooth muscle cells (VSMCs) in cerebral vessels (Bergmann et al. 1996). The anticonvulsant valproate has been shown to promote anti-apoptotic effects on human VSMCs in vitro through the Notch3/c-FLIP signalling pathway, with comparable in vivo effects on the signalling in the rat brain (Yuan et al. 2009). Furthermore, elevated plasma levels of inhibitory Notch ligands have been found in BD compared to healthy controls, suggesting that the Notch signalling pathway may be aberrantly attenuated in these disorders (Hoseth et al. 2018). Lithium may exert its mood stabilising effects by activating Notch signalling through the inhibition of

glycogen synthase kinase-3β (Espinosa et al. 2003, Hoseth et al. 2018). These findings highlight the possible relevance of these medications in the treatment of CADASIL and reducing the burden of white matter lesions in BD.

The diagnosis of BD, particularly BD type 2 is difficult, often being mistaken for unipolar depression. This may lead to inappropriate management and negative health outcomes including poor quality of life and suicide risk (Nasrallah 2015). Patients with CADASIL initially demonstrating only neurological symptoms may pose a further challenge to diagnosis. Pooled data from CADASIL case series that documented the presence of mood disorders showed that BD was reported in 9/451 (2%) of patients (Valenti et al. 2008). However, in these studies, psychiatric disorders in general were poorly characterised, usually lacking the usage of precise diagnostic criteria and thorough psychiatric evaluation (Valenti et al. 2008). Assessment of mood disorders in CADASIL using the DSM-IV semi-structured interview has demonstrated a higher frequency of BD than previously reported (Valenti et al. 2011). This raises the possibility that the diagnosis of BD may have been largely missed by non-psychiatric specialists in these larger series of patients (Valenti et al. 2011). Conversely, in psychiatric patients, CADASIL as a disease is likely to be underdiagnosed. If the affective symptoms present during psychiatric assessment without neurological deficits, the underlying diagnosis of CADASIL may not be recognised (Leyhe et al. 2005).

CONCLUSION

Altogether, based on these findings and with our clinical case in mind, it is therefore reasonable to emphasise that a thorough psychiatric evaluation should be carried out in patients with suspected CADASIL. Indeed, the possibility of this disease should be explored further by psychiatrists when assessing individuals presenting with features of psychiatric disorders such as BD who give a family history of strokes at an earlier age.

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Contribution of individual authors:

Rashid Zaman conceived the idea of the paper and wrote the case report and revised the manuscript.

Hong Kai Lim & Zachary A. Millar reviewed the literature and wrote the first draft.

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